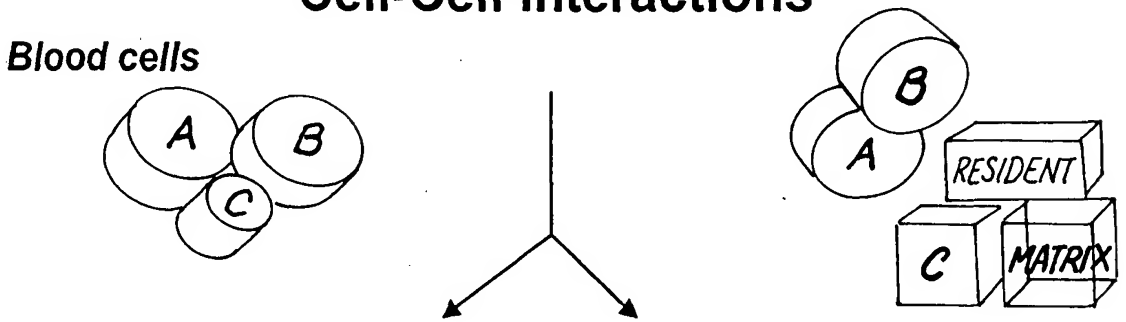
FIG. 1

Transcellular LM Biosynthesis

Cell-Cell Interactions



Amplification

Leukotrienes, Prostaglandins PAF, EETs , Novel Mediators

Proinflammatory Signals

Braking Signals

Lipoxins Novel Mediators , ATL

Antiinflammatory/ Resolution

FIG. 2A

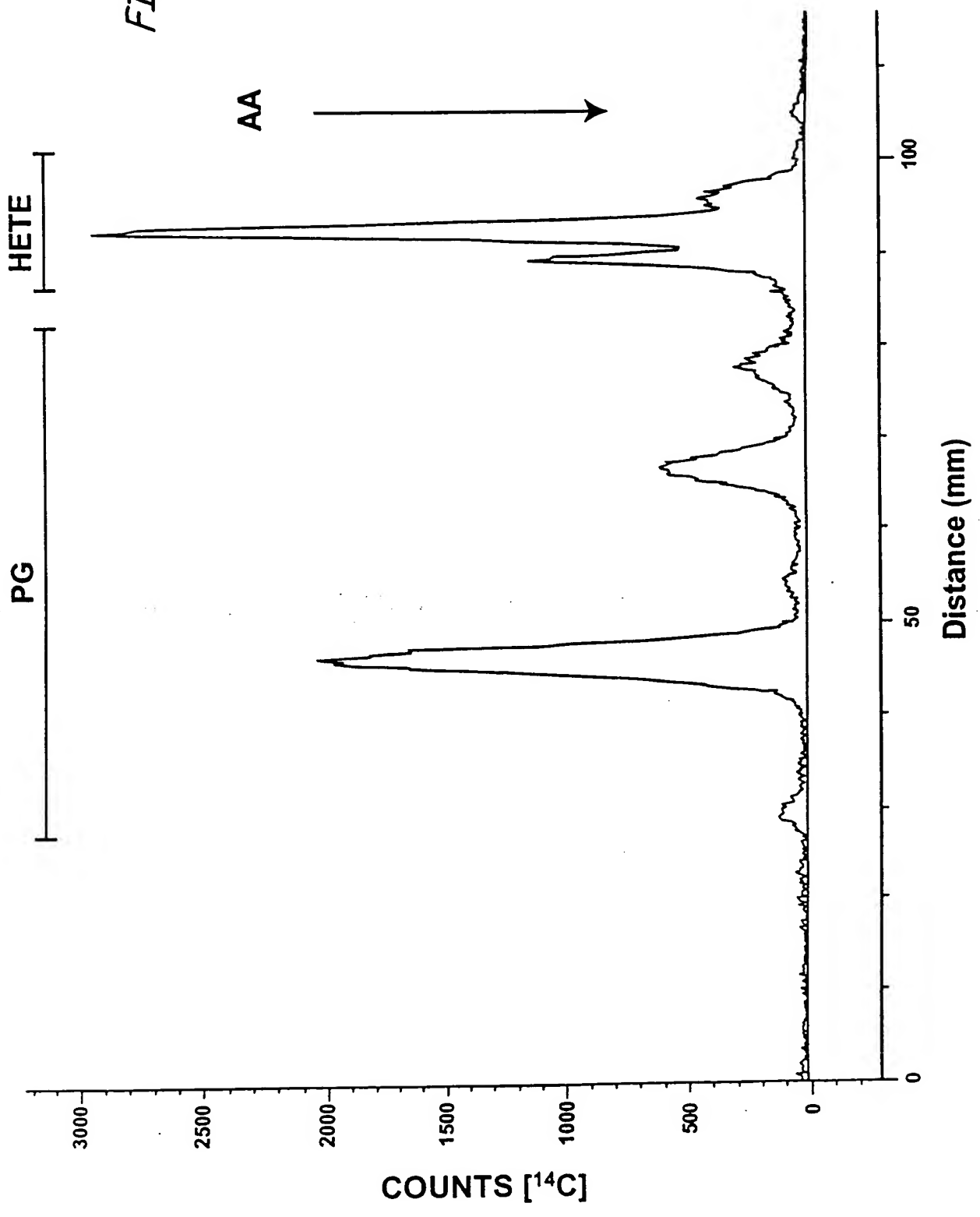

PG
HETE
AA
COUNTS [14C]
3000
2500
2000
1500
1000
500
0
0
50
100
Distance (mm)

FIG. 2B

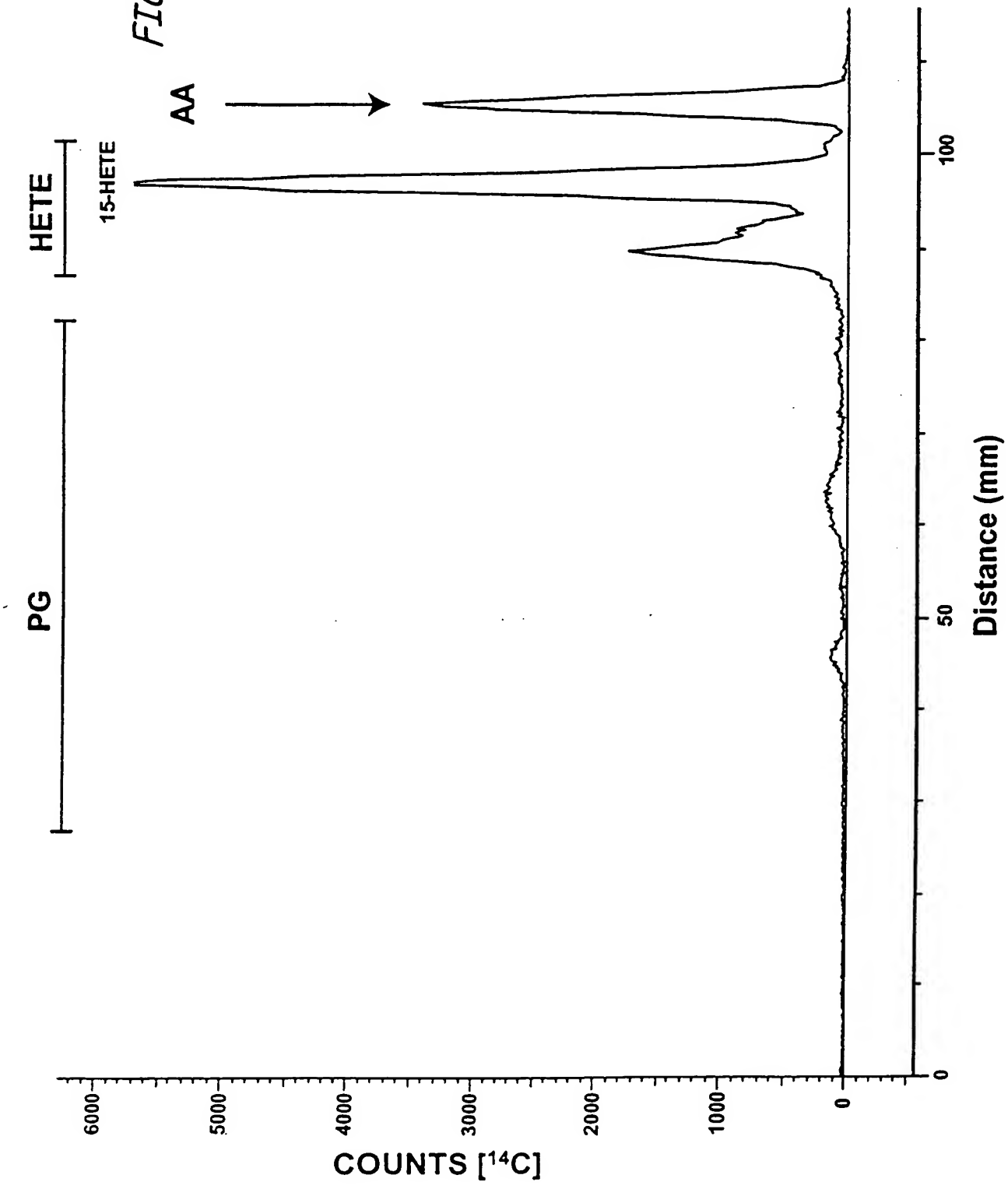

PG
HETE
15-HETE
AA
COUNTS [14C]
6000
5000
4000
3000
2000
1000
0
0
50
100
Distance (mm)

FIG. 2C

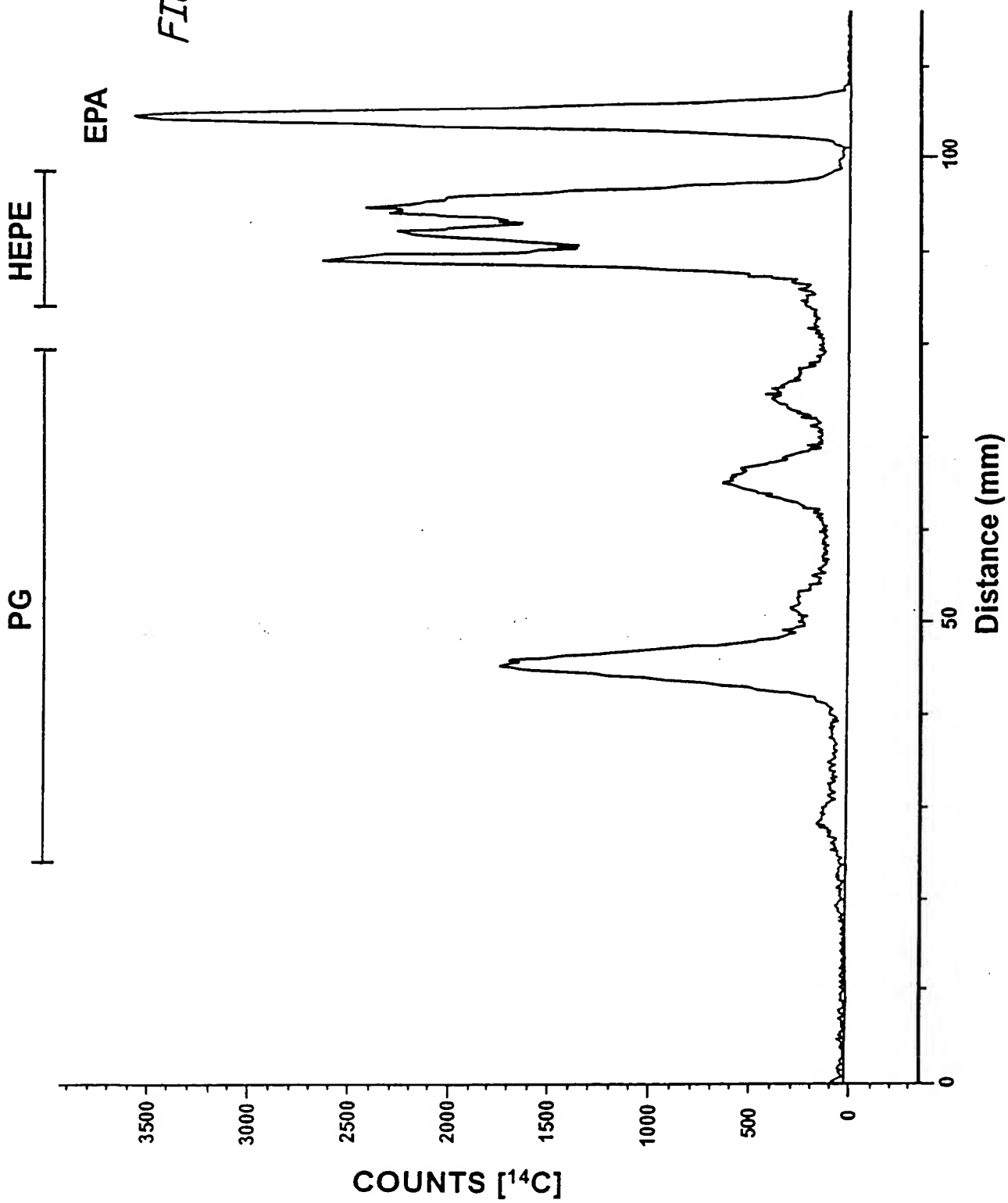

PG
HEPE
EPA
COUNTS [14C]
3500
3000
2500
2000
1500
1000
500
0
0
50
100
Distance (mm)

FIG. 2D

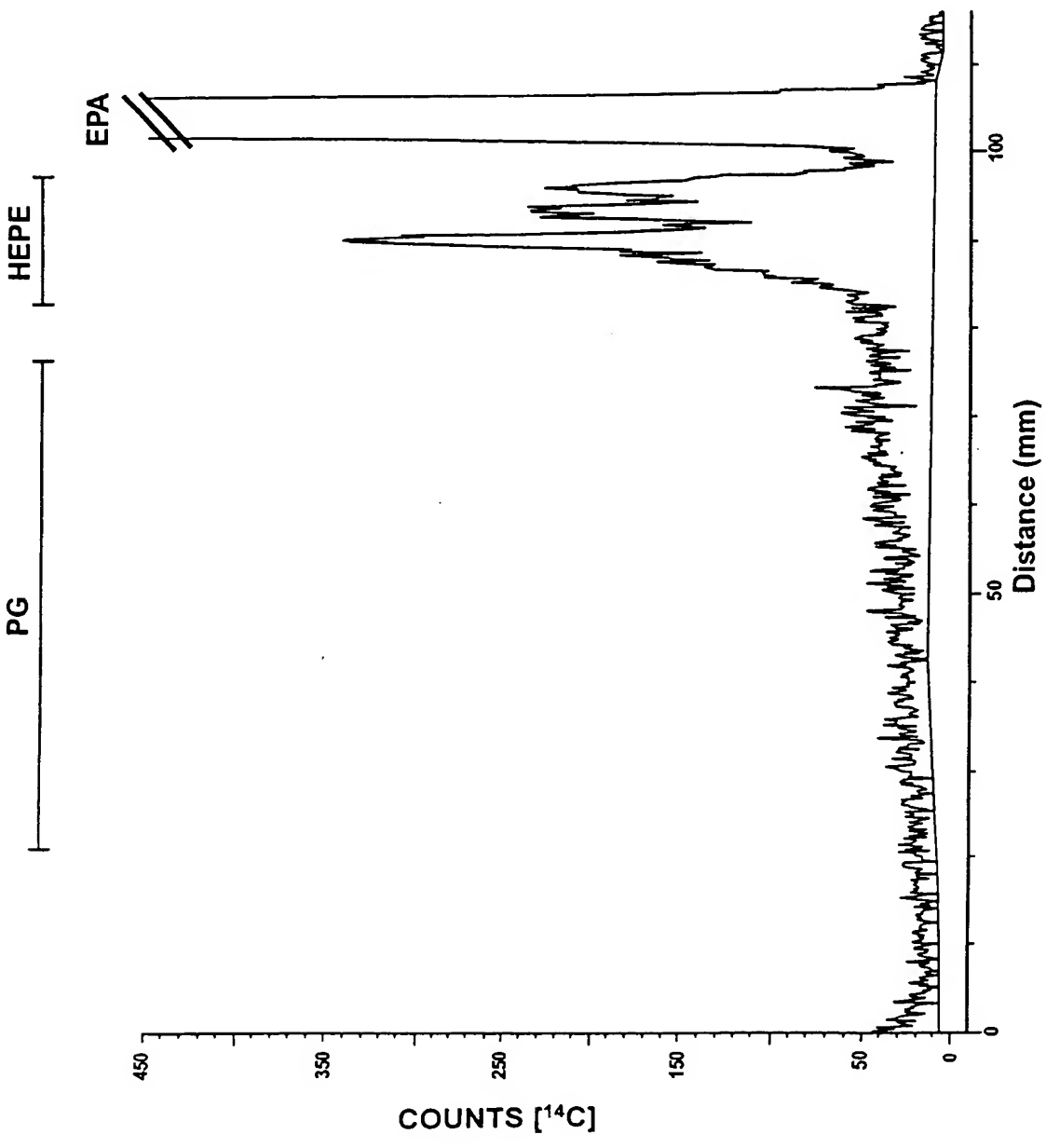


FIG. 3A

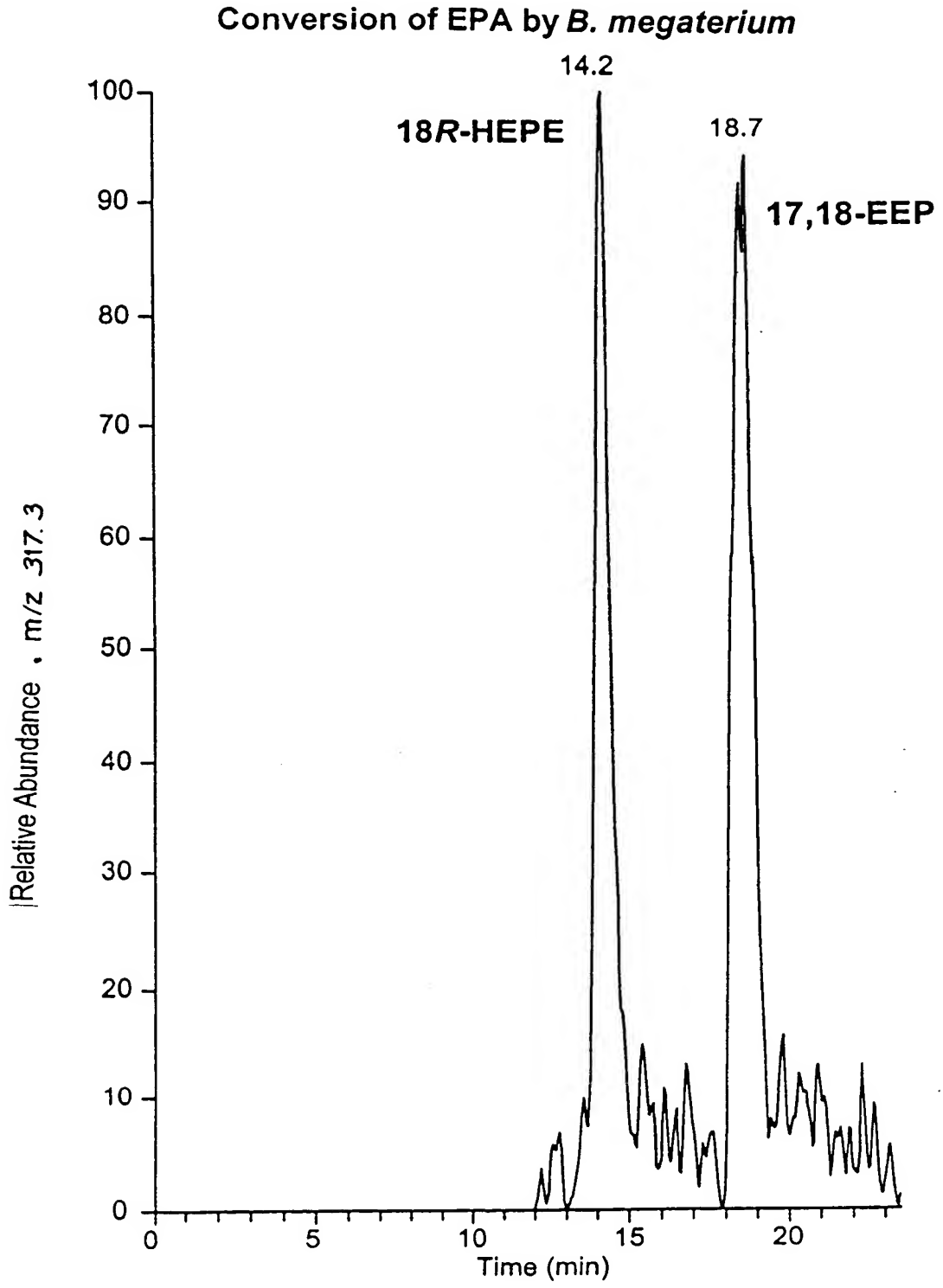

Conversion of EPA by B. megaterium
14.2
18R-HEPE
18.7
17,18-EEP
Relative Abundance • m/z 317.3
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
Time (min)

FIG. 3B

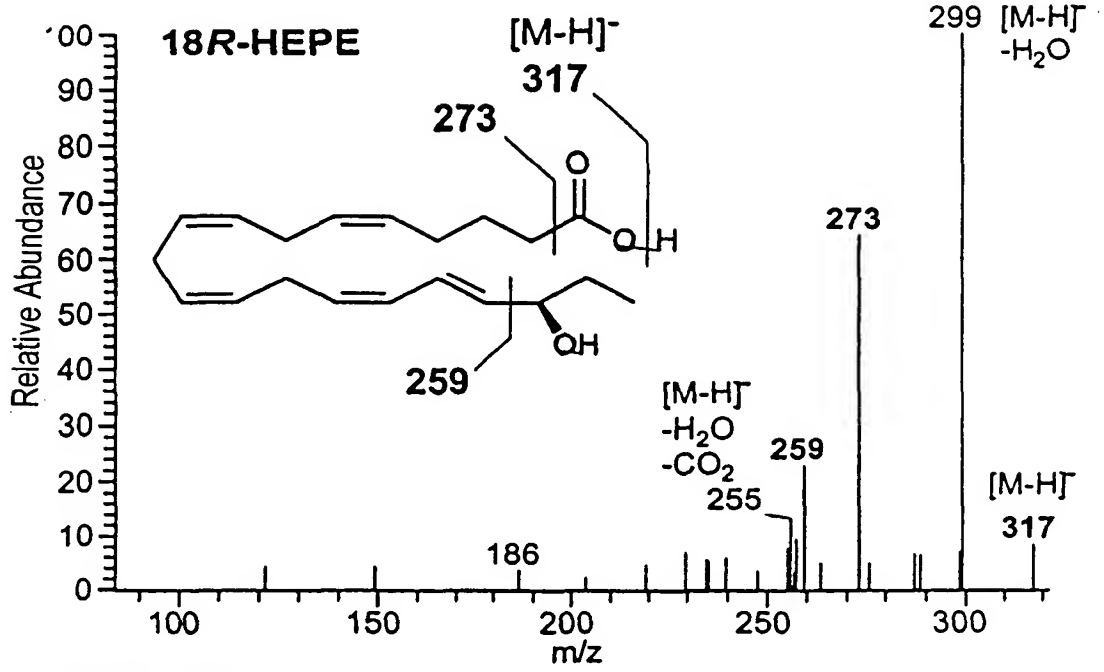

Conversion of EPA by B. megaterium
18R-HEPE
[M-H]⁻
317
273
259
299 [M-H]⁻ -H2O
273
[M-H]⁻ -H2O -CO2
259
255
[M-H]⁻
317
186
Relative Abundance
m/z

FIG. 3C

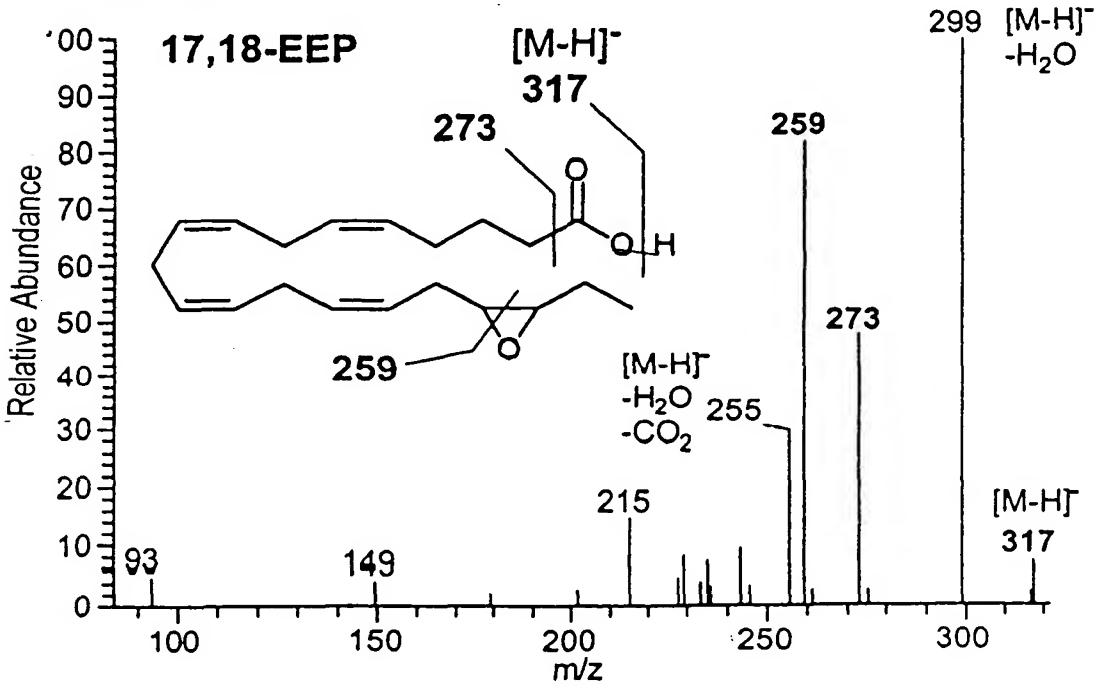

17,18-EEP
[M-H]⁻
317
273
259
299 [M-H]⁻ -H2O
259
273
[M-H]⁻ -H2O -CO2
255
215
[M-H]⁻
317
93
149
Relative Abundance
m/z

FIG. 4A

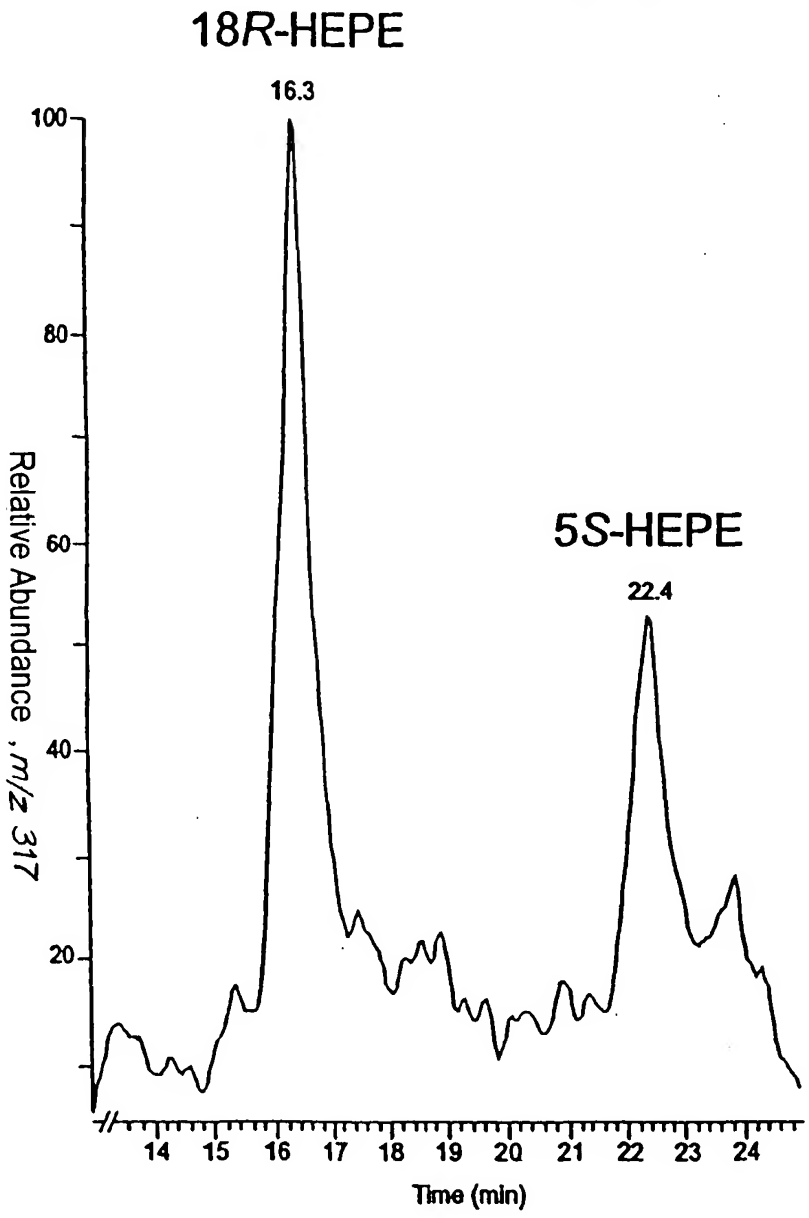


FIG. 4B

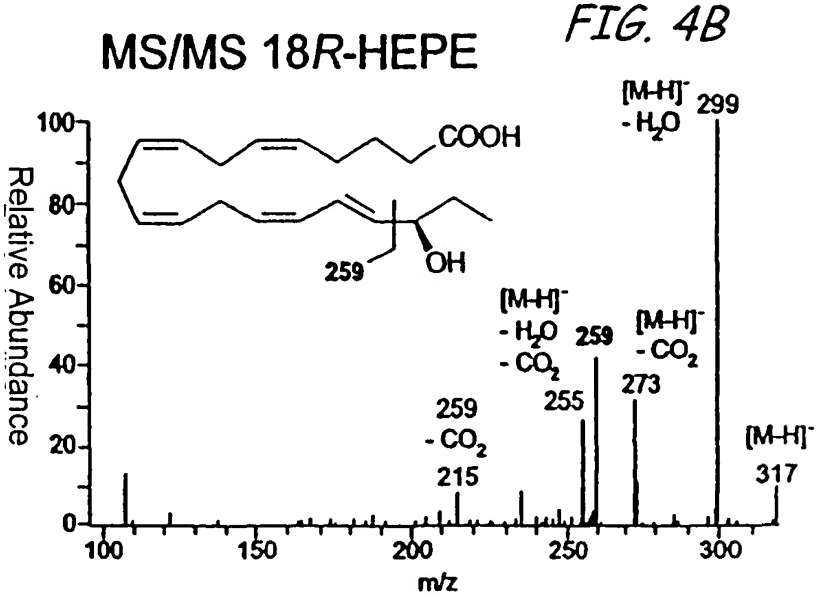


FIG. 4C

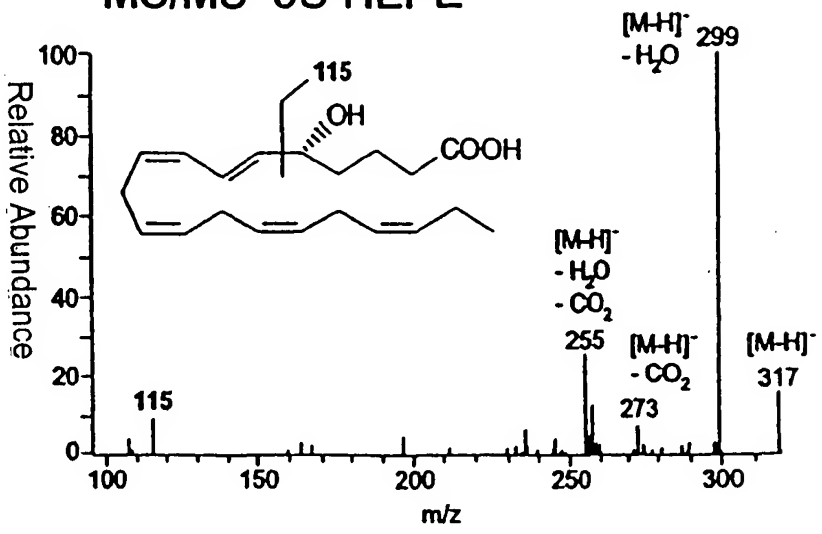


FIG. 4D

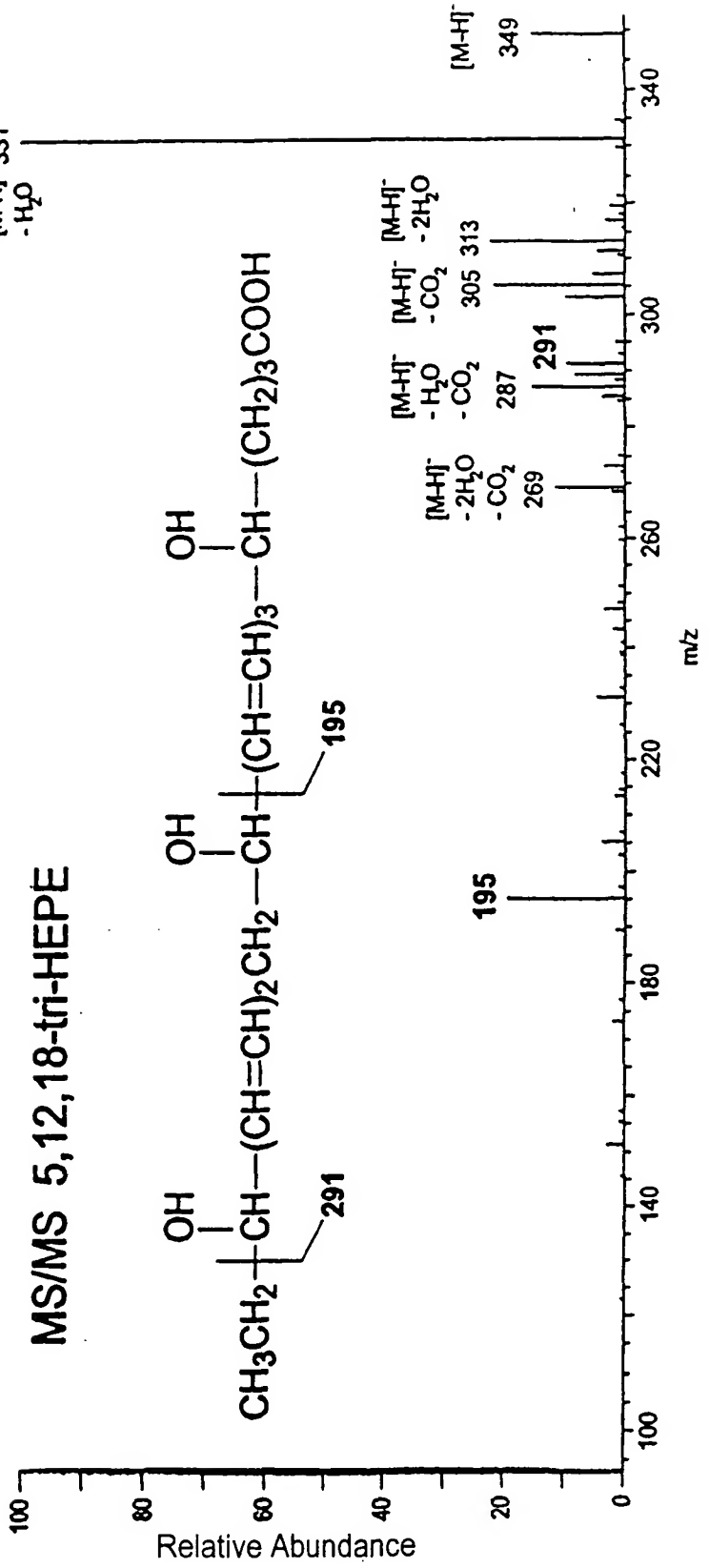

MS/MS 5,12,18-tri-HEPE
CH3CH2
OH
CH
(CH=CH)2CH2
OH
CH
(CH=CH)3
OH
CH
(CH2)3COOH
291
195
[M-H]- 331
-H2O
[M-H]- 349
[M-H]- -2H2O 313
[M-H]- -CO2 305
[M-H]- -H2O -CO2 287
291
[M-H]- -2H2O -CO2 269
195
Relative Abundance
m/z
100
80
60
40
20
0
100
140
180
220
260
300
340

FIG. 5A MS 5,12,18-tri-HEPE from B. megaterium

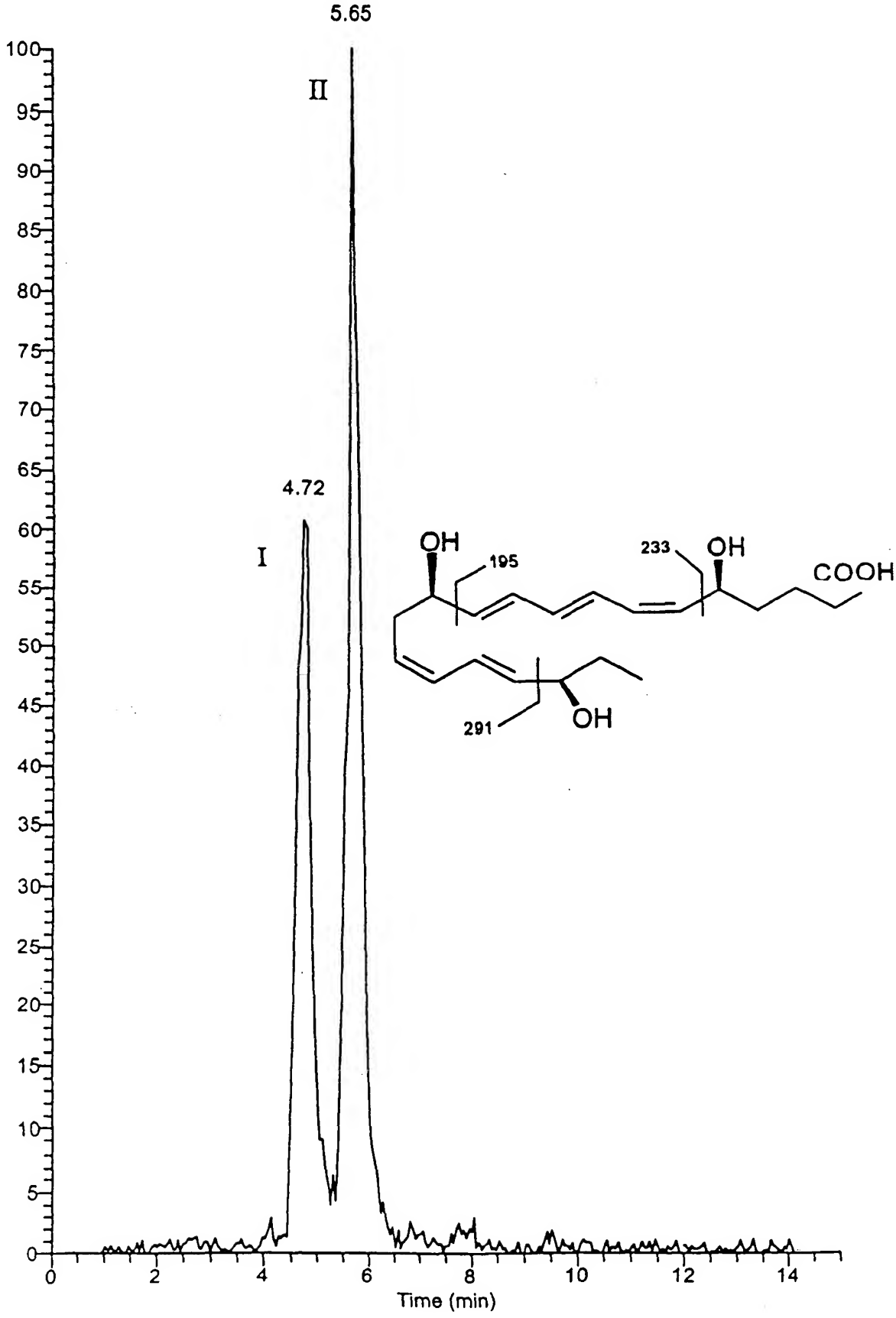


FIG. 5B

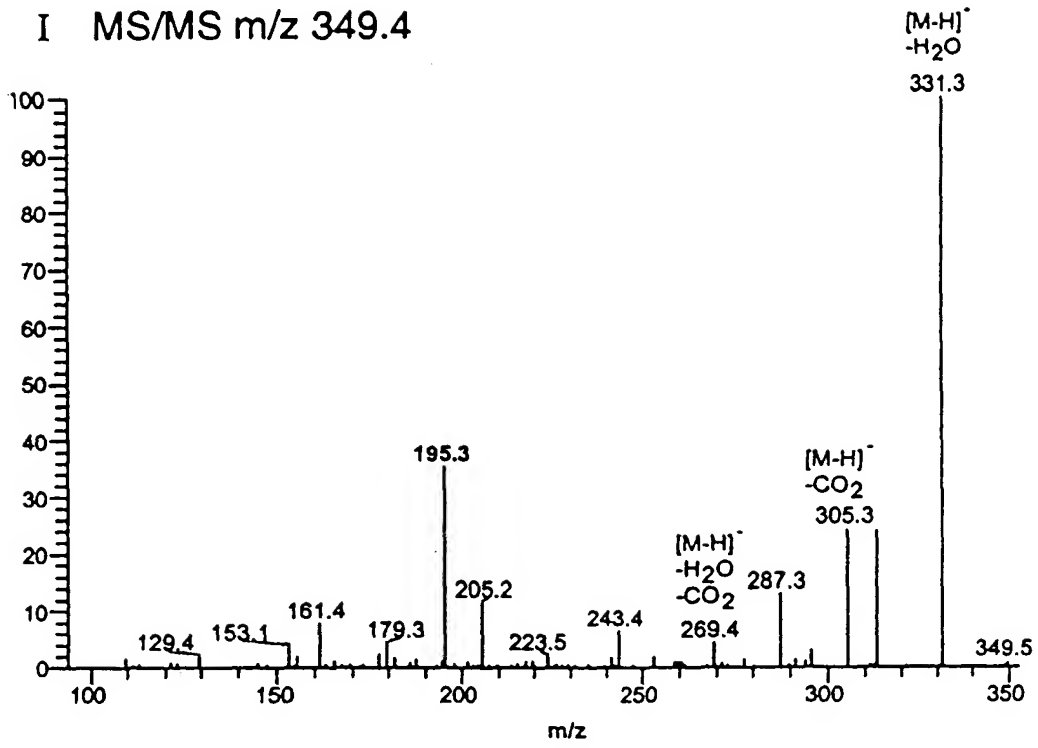

I MS/MS m/z 349.4
[M-H]⁻ -H2O
331.3
195.3
[M-H]⁻ -CO2
305.3
[M-H]⁻ -H2O -CO2
287.3
205.2
161.4
179.3
243.4
269.4
129.4
153.1
223.5
349.5
100
150
200
250
300
350
m/z

FIG. 5C

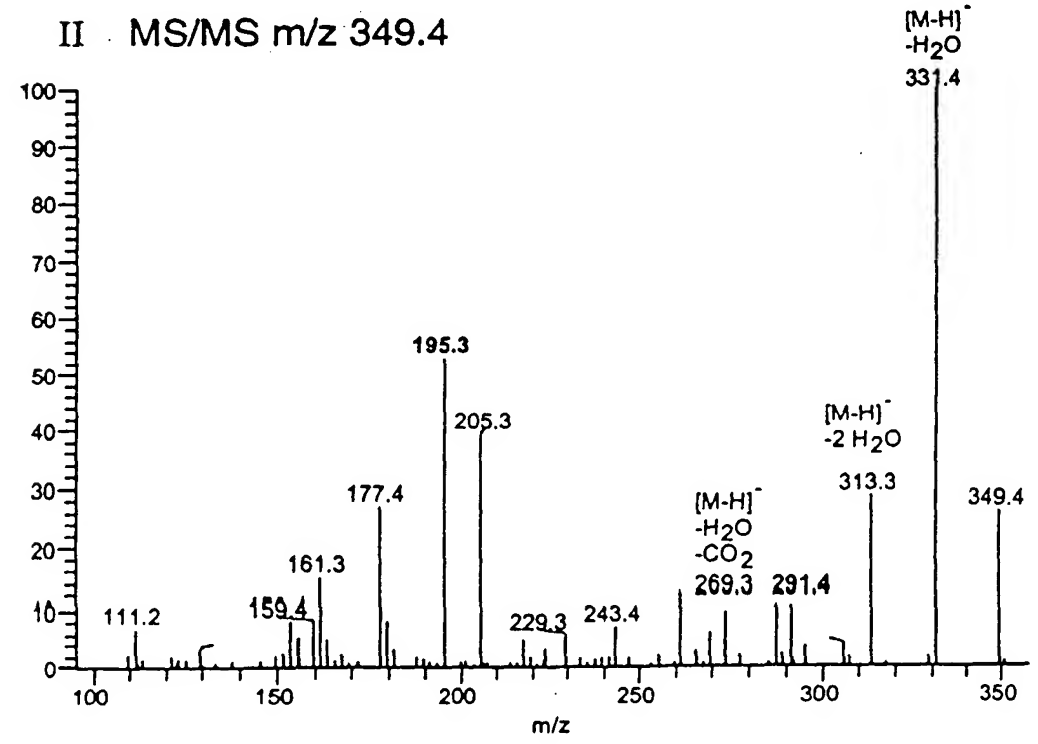

II MS/MS m/z 349.4
[M-H]⁻ -H2O
331.4
195.3
205.3
[M-H]⁻ -2 H2O
313.3
177.4
[M-H]⁻ -H2O -CO2
269.3
291.4
349.4
161.3
159.4
111.2
229.3
243.4
100
150
200
250
300
350
m/z

FIG. 6

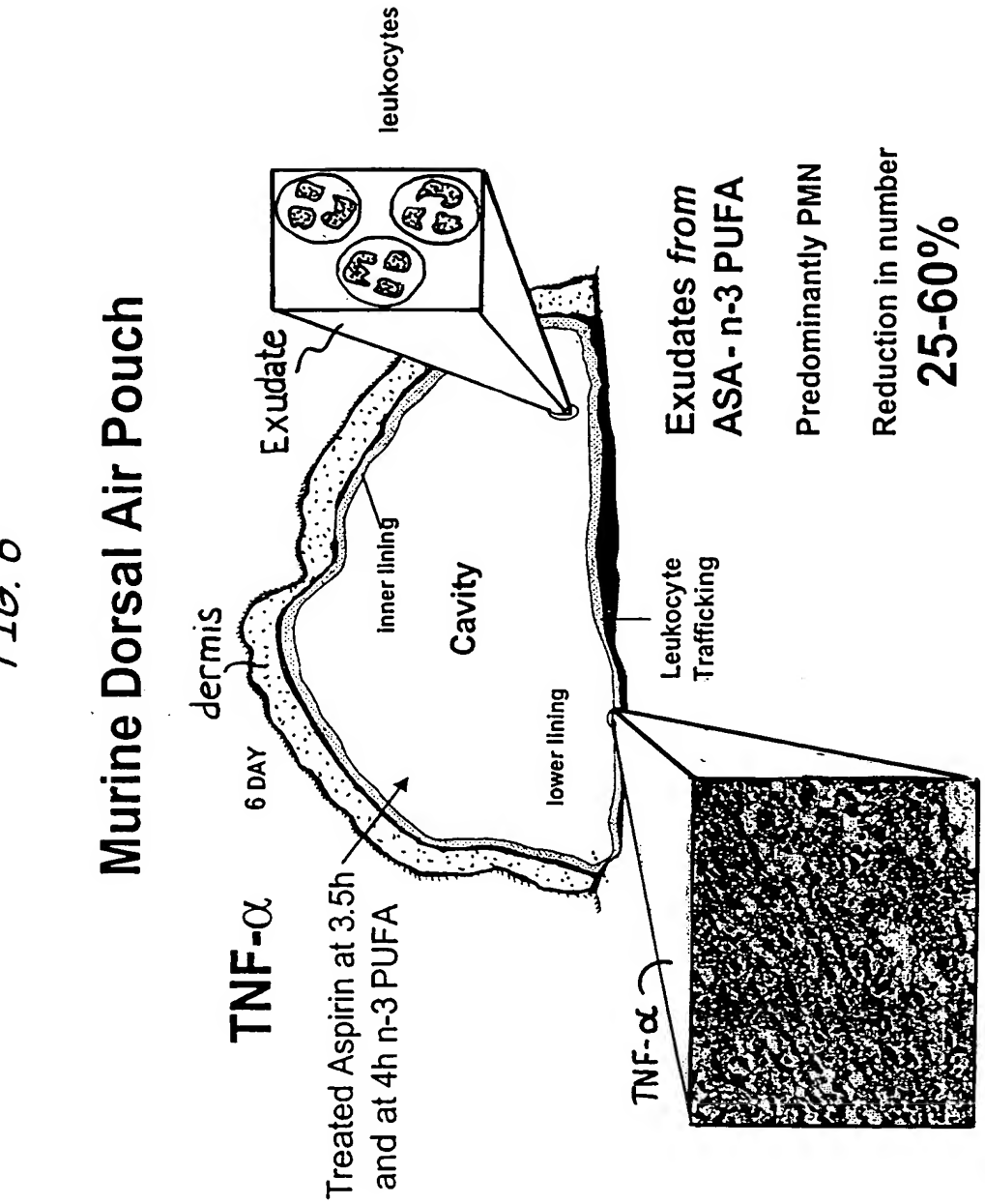

Murine Dorsal Air Pouch
TNF-α
6 DAY
dermis
Exudate
leukocytes
Inner lining
Cavity
lower lining
Treated Aspirin at 3.5h
and at 4h n-3 PUFA
Leukocyte
Trafficking
TNF-α
Exudates from
ASA - n-3 PUFA
Predominantly PMN
Reduction in number
25-60%

FIG. 7A

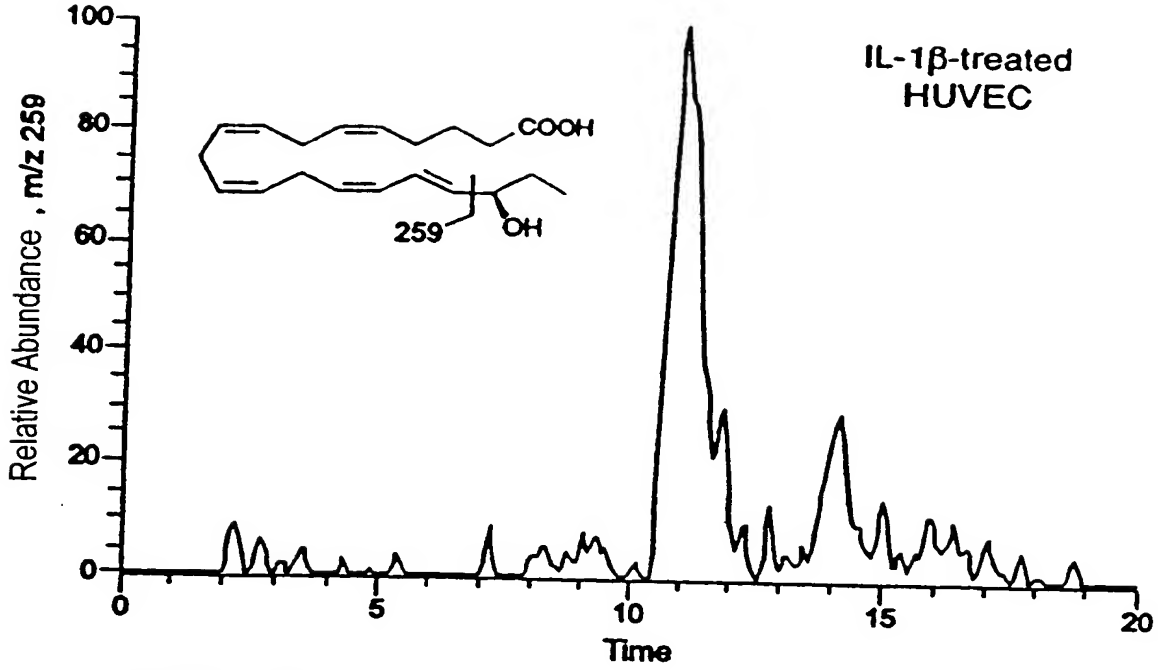

Relative Abundance , m/z 259
100
80
60
40
20
0
0
5
10
15
20
Time
COOH
259
OH
IL-1β-treated
HUVEC

FIG. 7C

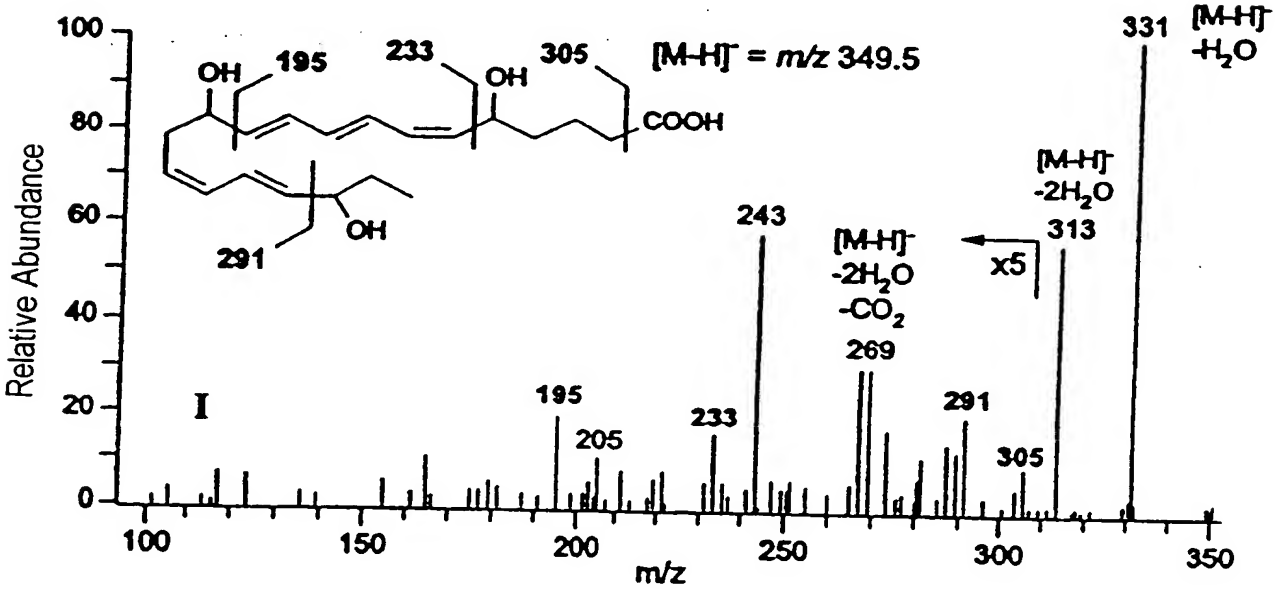

Relative Abundance
100
80
60
40
20
0
100
150
200
250
300
350
m/z
OH
195
233
OH
305
COOH
291
OH
[M-H]⁻ = m/z 349.5
331
[M-H]⁻
-H2O
[M-H]⁻
-2H2O
313
243
[M-H]⁻
-2H2O
-CO2
269
x5
I
195
205
233
291
305

FIG. 7B

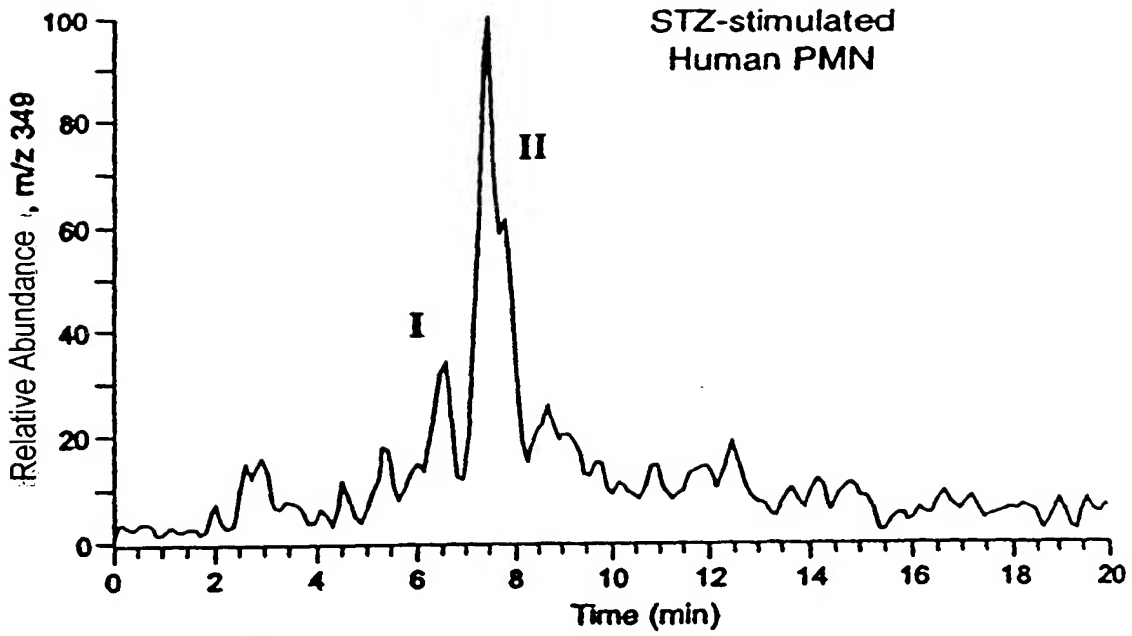

STZ-stimulated
Human PMN
Relative Abundance, m/z 349
Time (min)
I
II

FIG. 7D

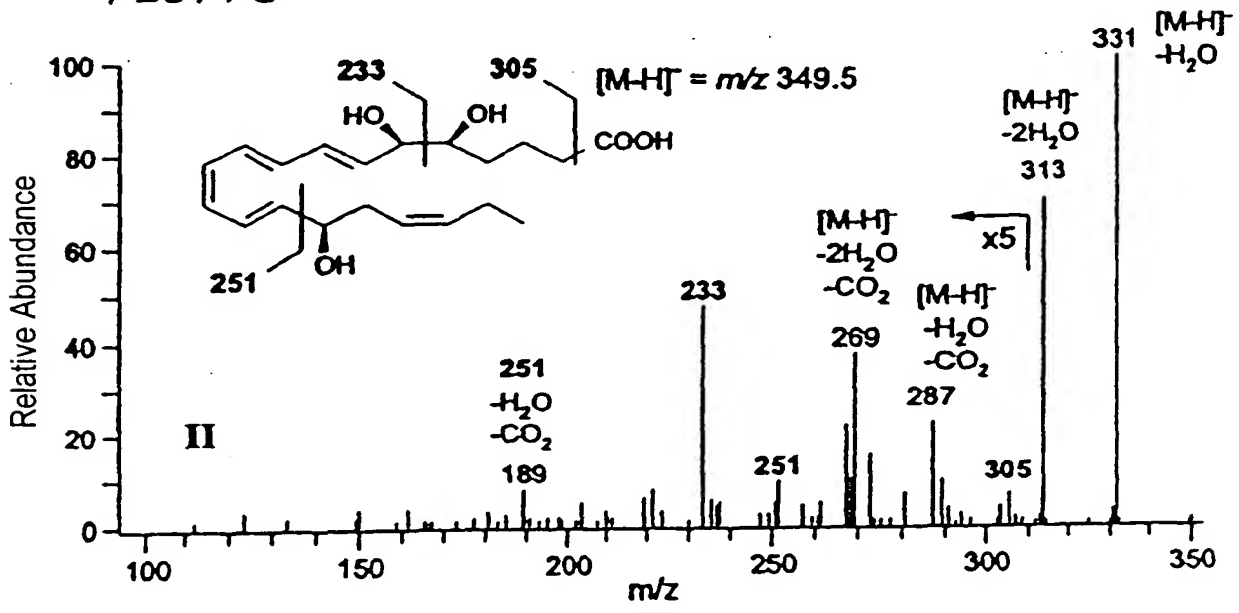

[M-H]⁻ = m/z 349.5
233
305
HO
OH
COOH
251
OH
II
Relative Abundance
m/z
331
[M-H]⁻ -H2O
[M-H]⁻ -2H2O
313
[M-H]⁻ -2H2O -CO2
x5
[M-H]⁻ -H2O -CO2
269
287
233
251 -H2O -CO2
189
251
305

FIG. 8A

Mono-HEPES: Enzymatic Products from Acetylated COX 2 and EPA

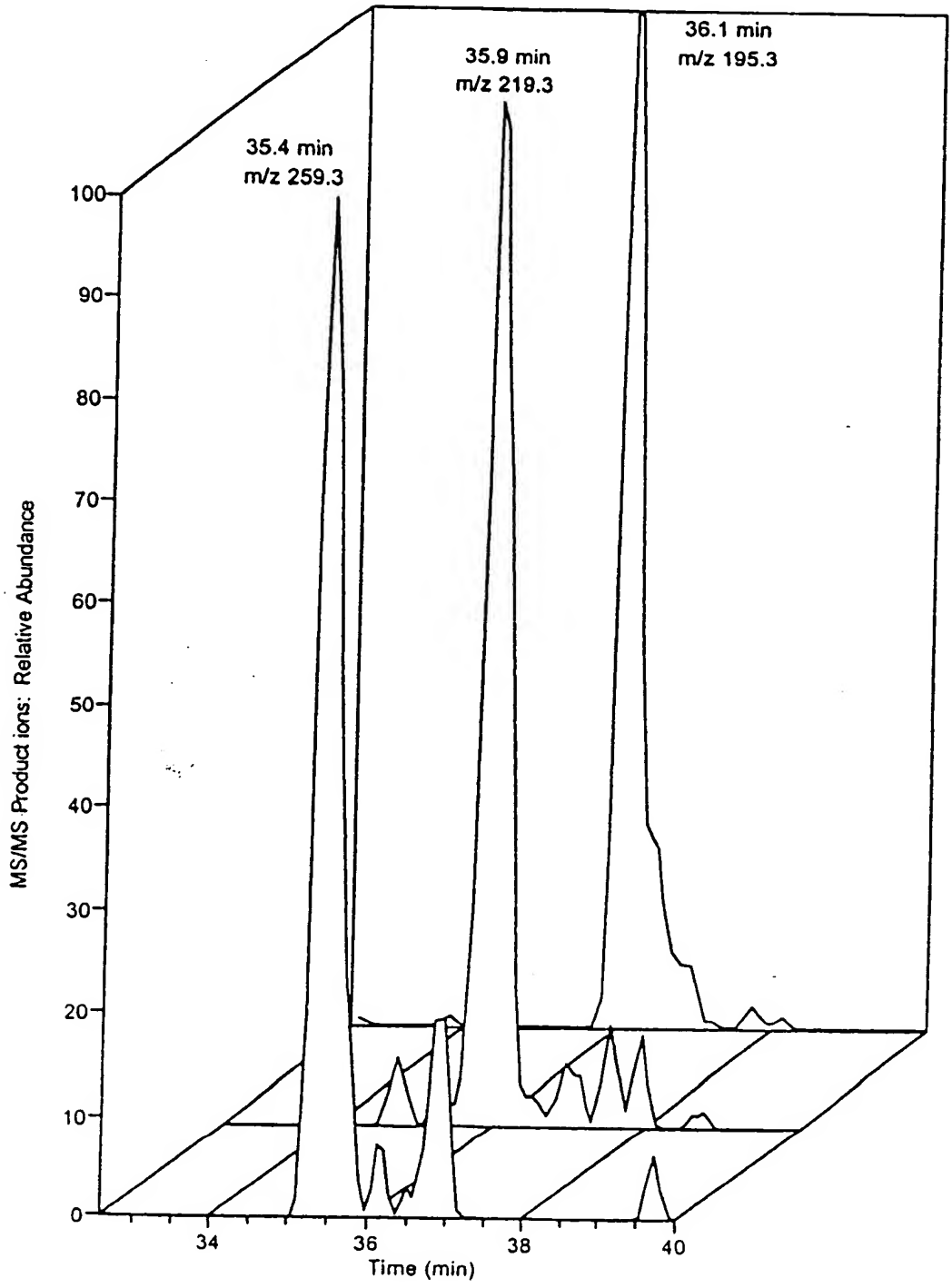


FIG. 8B

Mono-HEPES: Enzymatic Products from Acetylated COX 2 and EPA

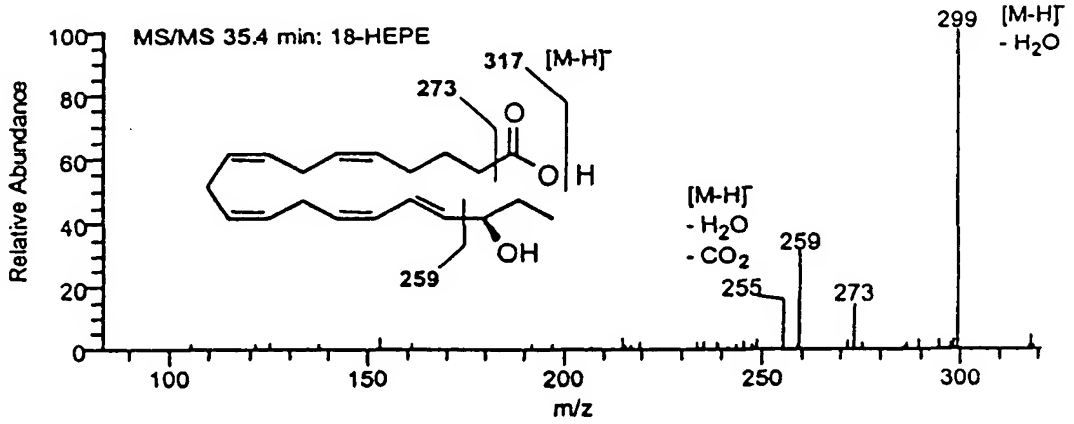


FIG. 8C

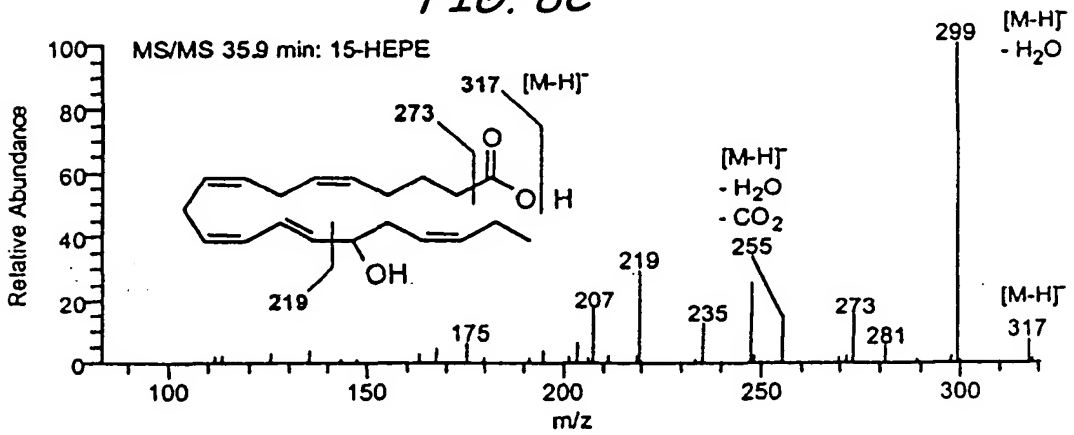


FIG. 8D

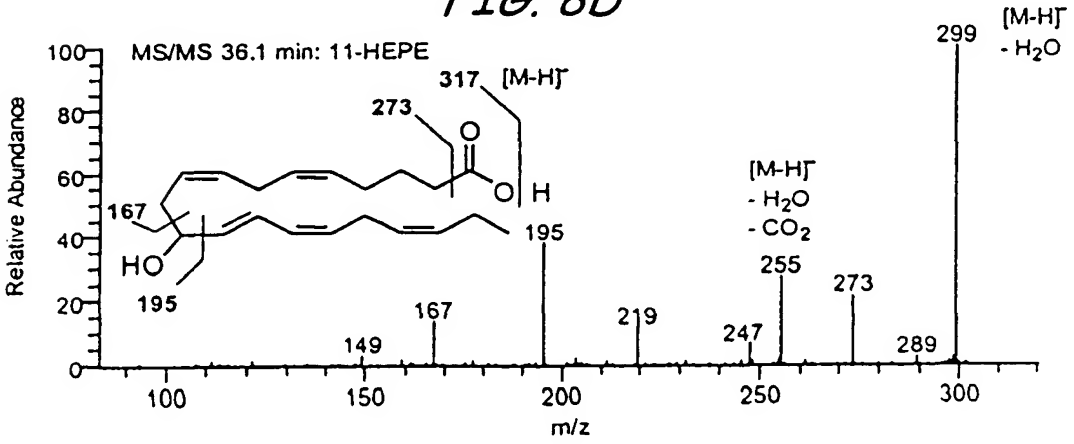


FIG. 9A

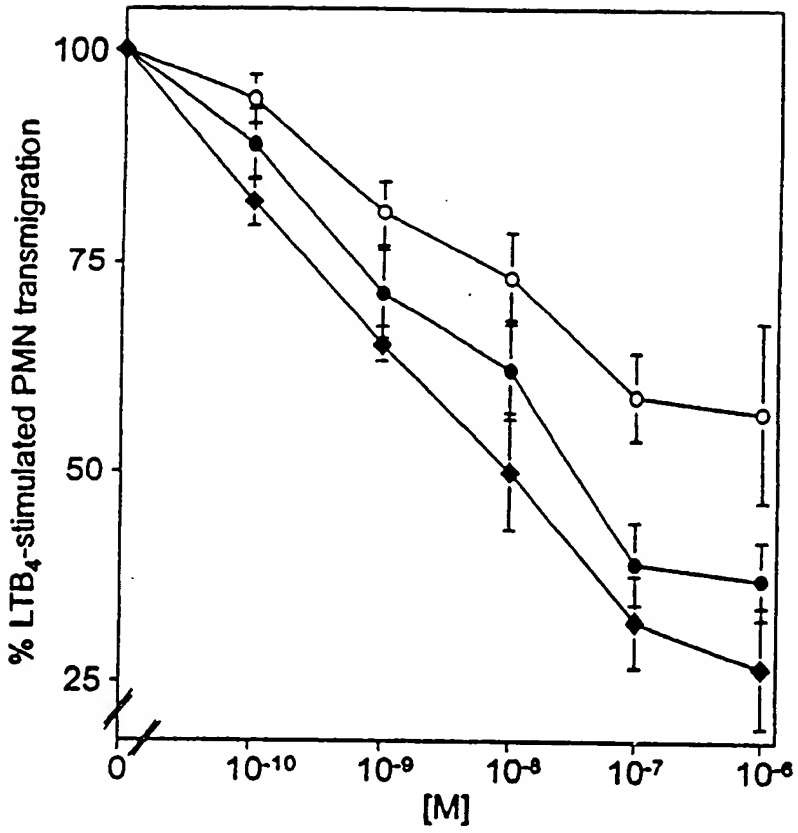

100
75
50
25
0
10^{-10}
10^{-9}
10^{-8}
10^{-7}
10^{-6}
[M]
% LTB_4-stimulated PMN transmigration

FIG. 9B

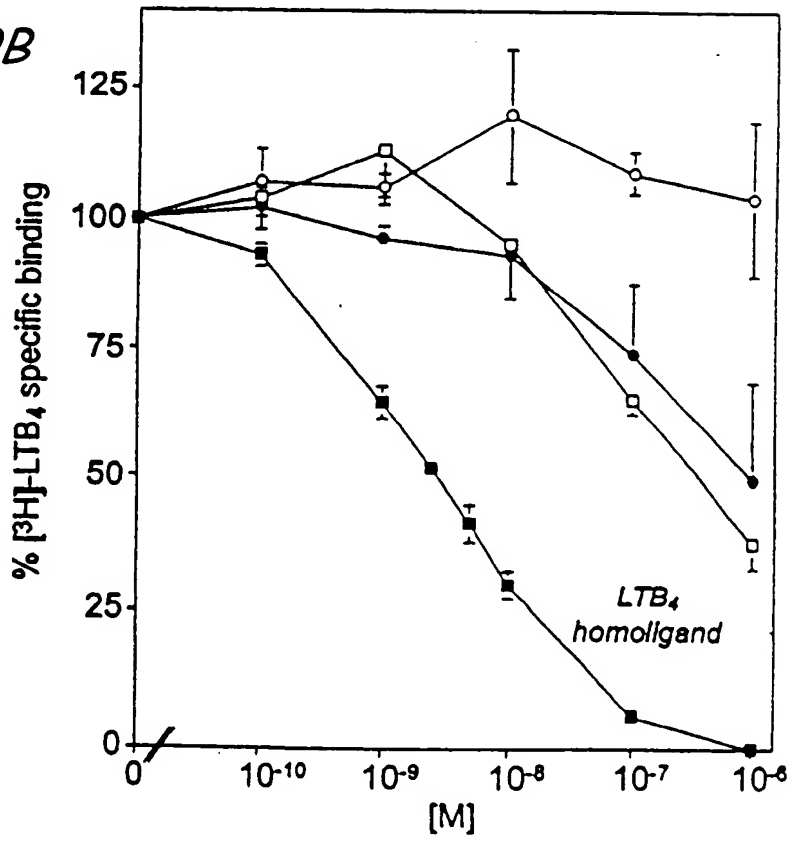

125
100
75
50
25
0
10^{-10}
10^{-9}
10^{-8}
10^{-7}
10^{-6}
[M]
% [^{3}H]-LTB_4 specific binding
LTB_4
homoligand

FIG. 9C

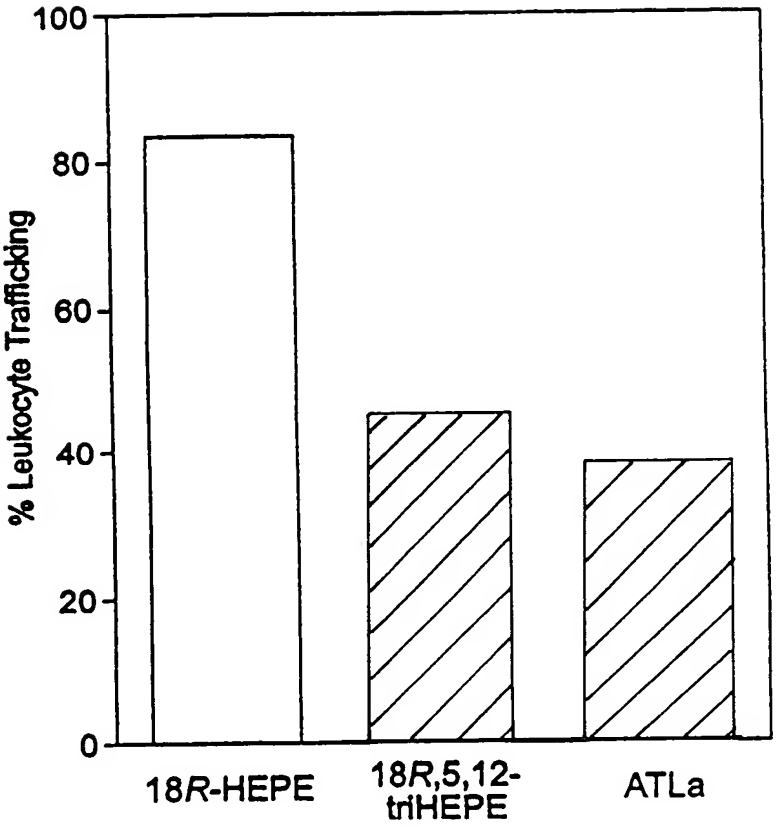

100
80
60
40
20
0
% Leukocyte Trafficking
18R-HEPE
18R,5,12-triHEPE
ATLa

FIG. 10A

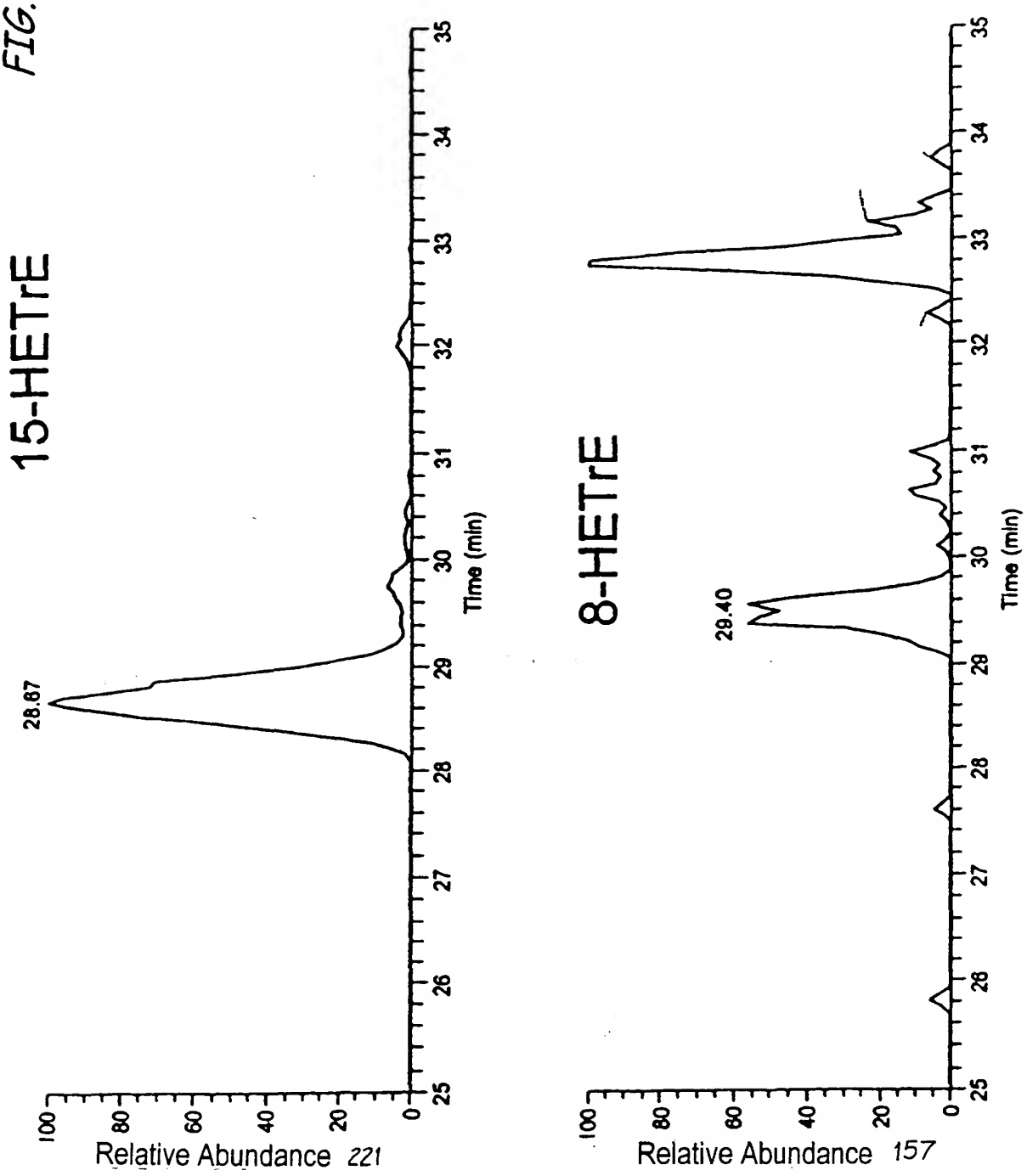

15-HETrE
28.87
Relative Abundance 221
Time (min)
8-HETrE
29.40
Relative Abundance 157
Time (min)

FIG. 10B

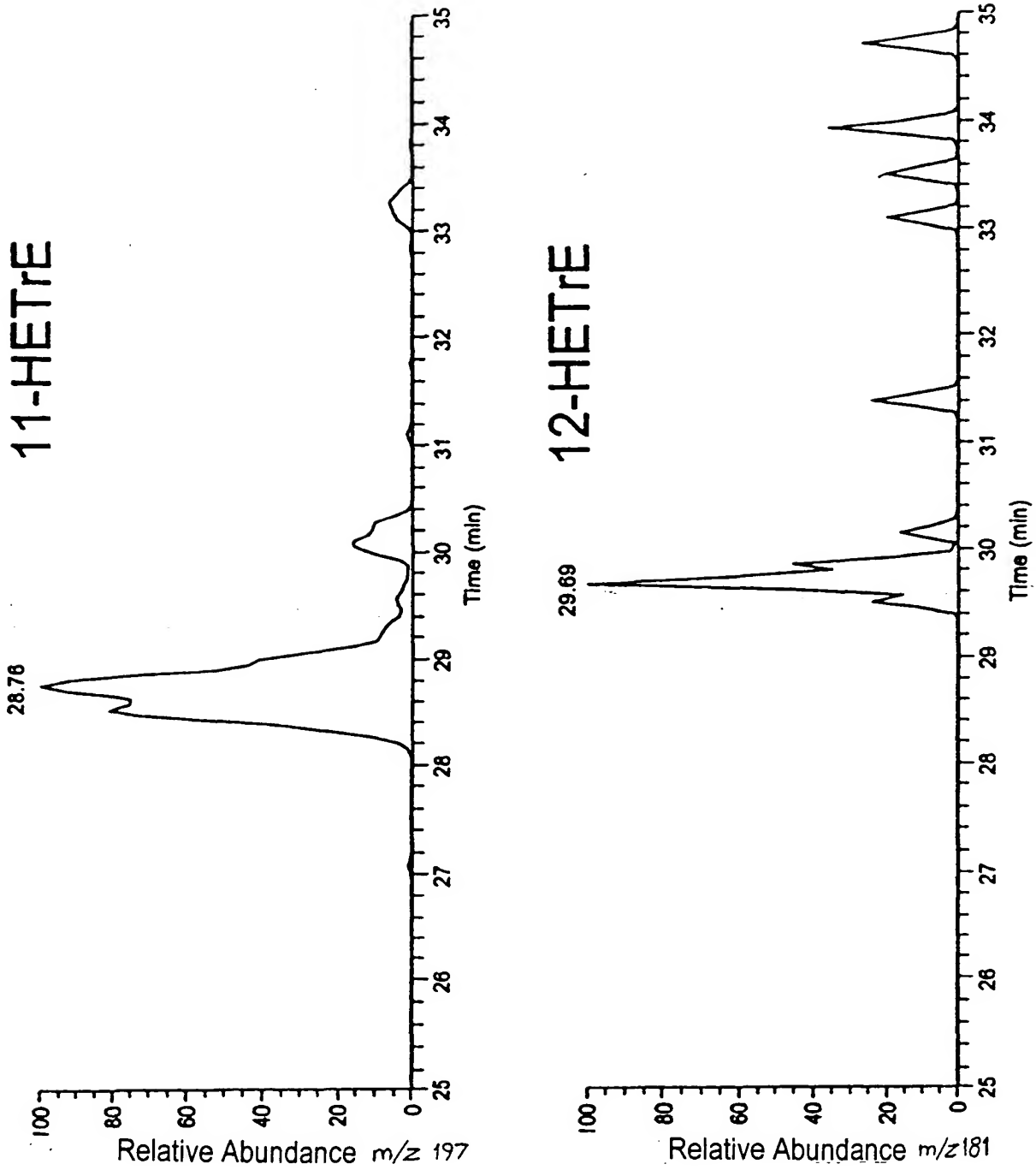
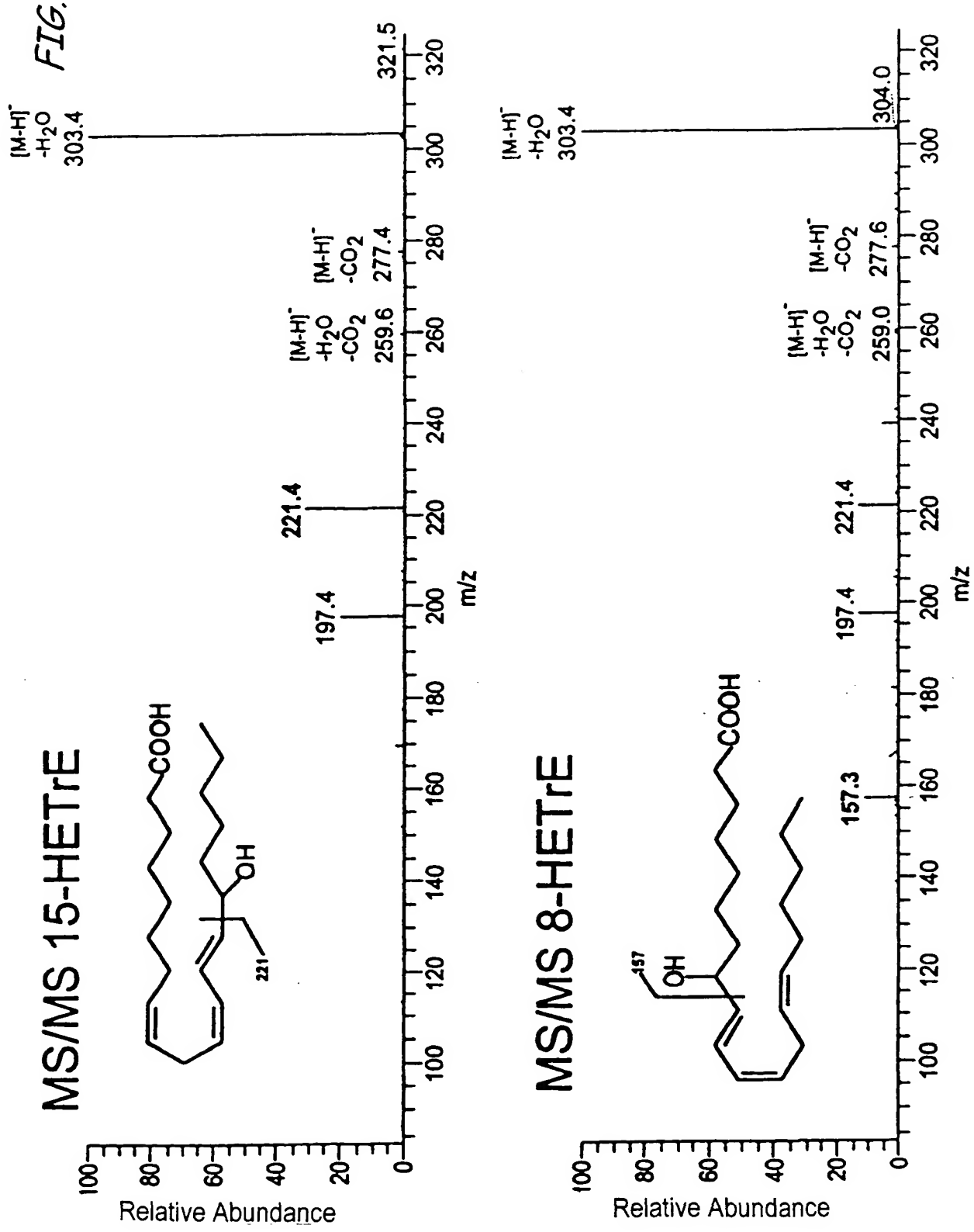

11-HETrE
28.76
Relative Abundance m/z 197
Time (min)
12-HETrE
29.69
Relative Abundance m/z 181
Time (min)

FIG. 10C


MS/MS 15-HETrE
COOH
OH
221
[M-H]⁻ -H2O 303.4
197.4
221.4
[M-H]⁻ -H2O -CO2 259.6
[M-H]⁻ -CO2 277.4
321.5
m/z
Relative Abundance
MS/MS 8-HETrE
COOH
OH
157
[M-H]⁻ -H2O 303.4
157.3
197.4
221.4
[M-H]⁻ -H2O -CO2 259.0
[M-H]⁻ -CO2 277.6
304.0
m/z
Relative Abundance

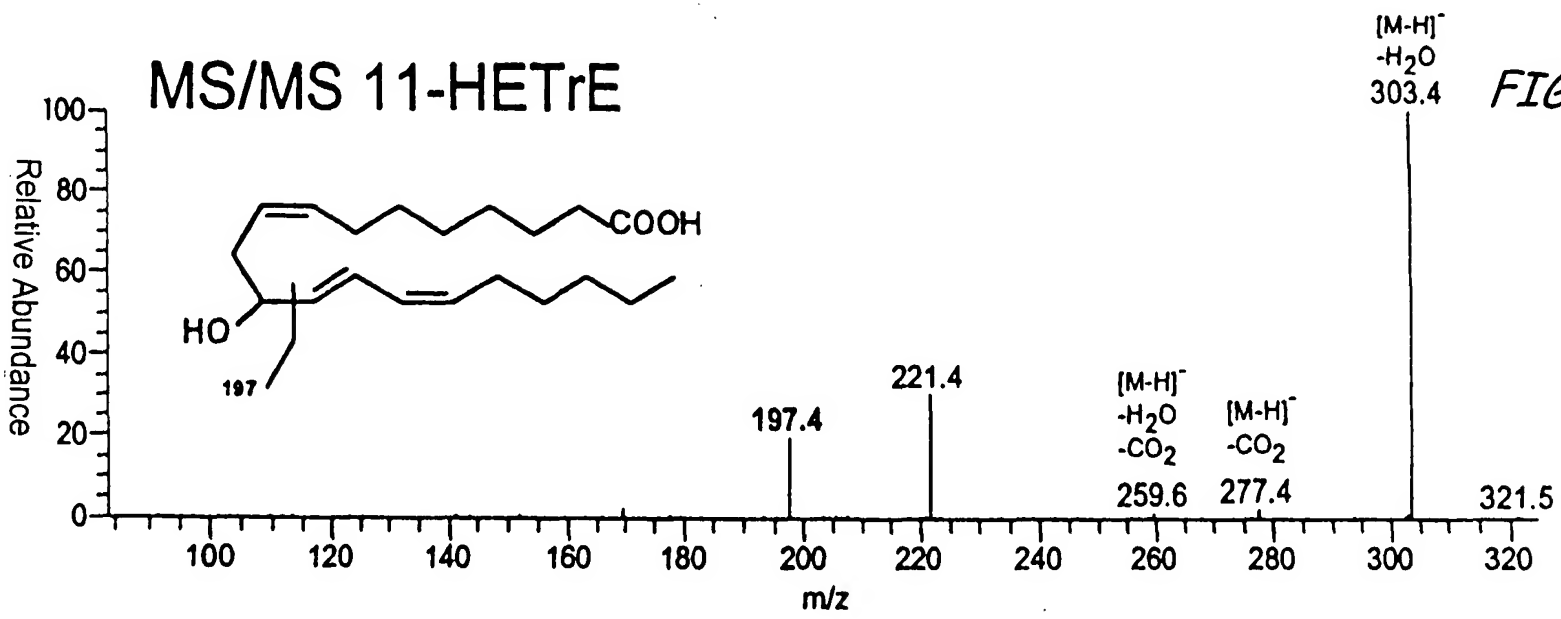

MS/MS 11-HETrE
Relative Abundance
m/z
COOH
HO
197
197.4
221.4
[M-H]⁻ -H2O -CO2
259.6
[M-H]⁻ -CO2
277.4
[M-H]⁻ -H2O
303.4
321.5

FIG. 10D

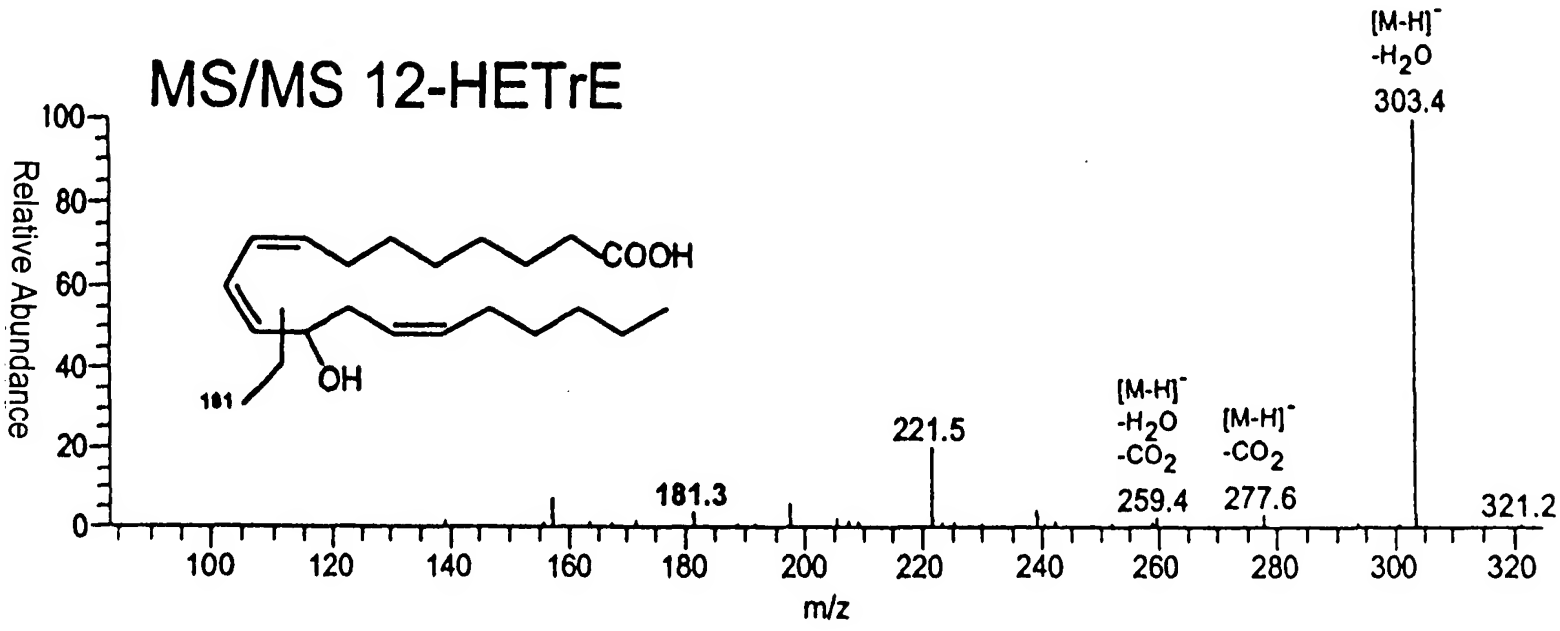

MS/MS 12-HETrE
Relative Abundance
m/z
COOH
OH
181
181.3
221.5
[M-H]⁻ -H2O -CO2
259.4
[M-H]⁻ -CO2
277.6
[M-H]⁻ -H2O
303.4
321.2

FIG. 10E

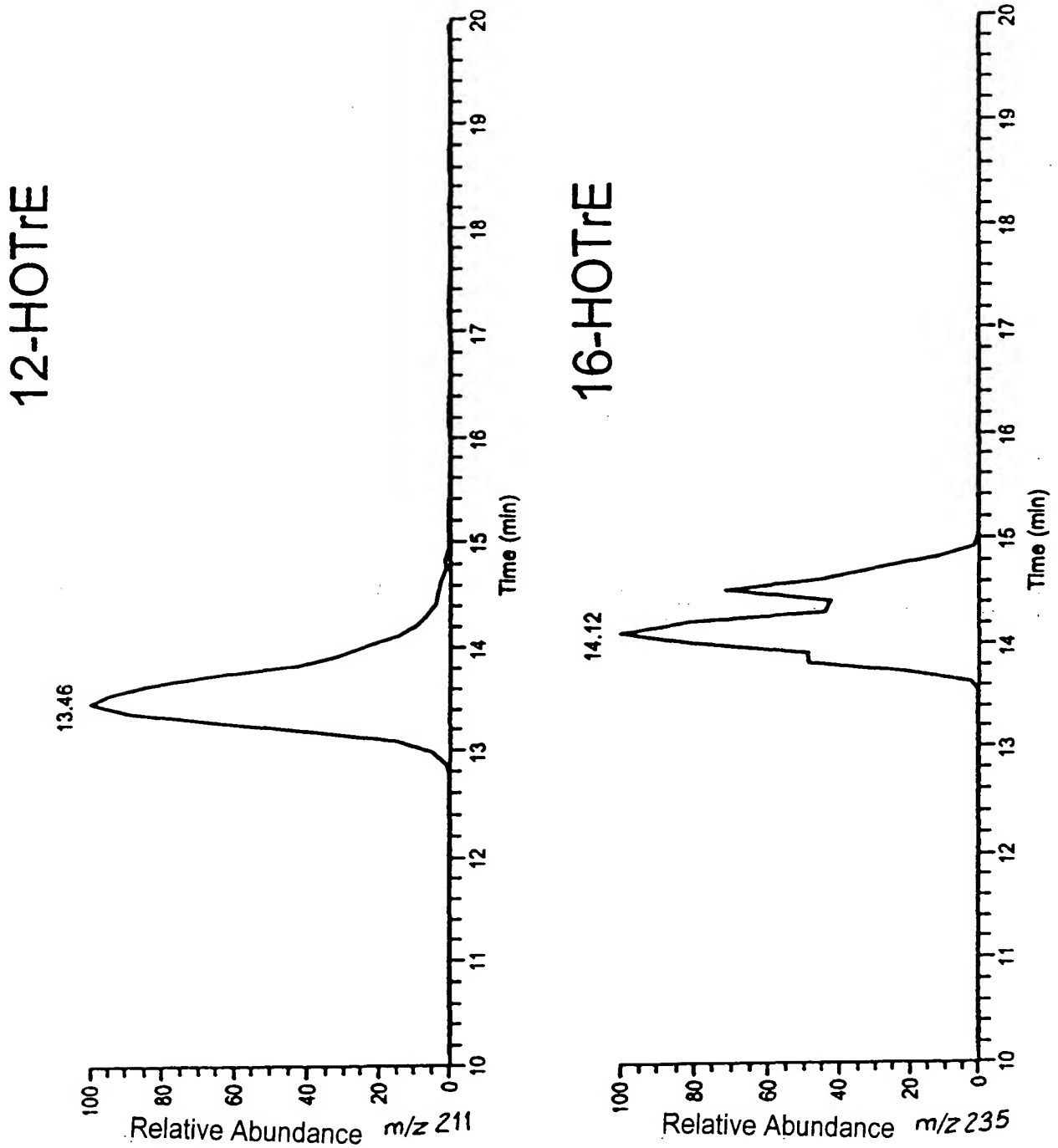
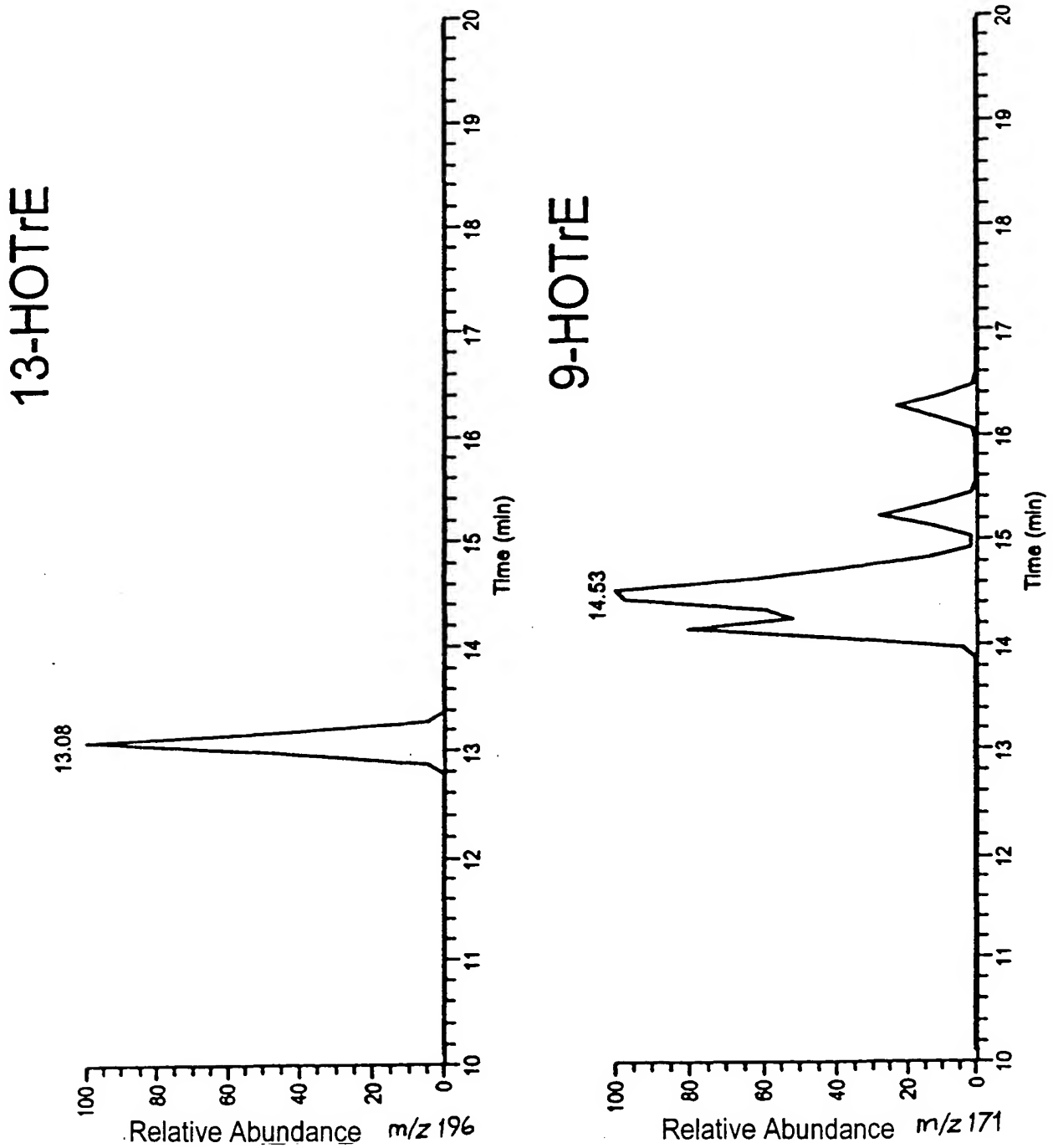

12-HOTrE
13.46
Relative Abundance
m/z 211
Time (min)
16-HOTrE
14.12
Relative Abundance
m/z 235
Time (min)

FIG. 10F


13-HOTrE
13.08
Relative Abundance
m/z 196
Time (min)
9-HOTrE
14.53
Relative Abundance
m/z 171
Time (min)

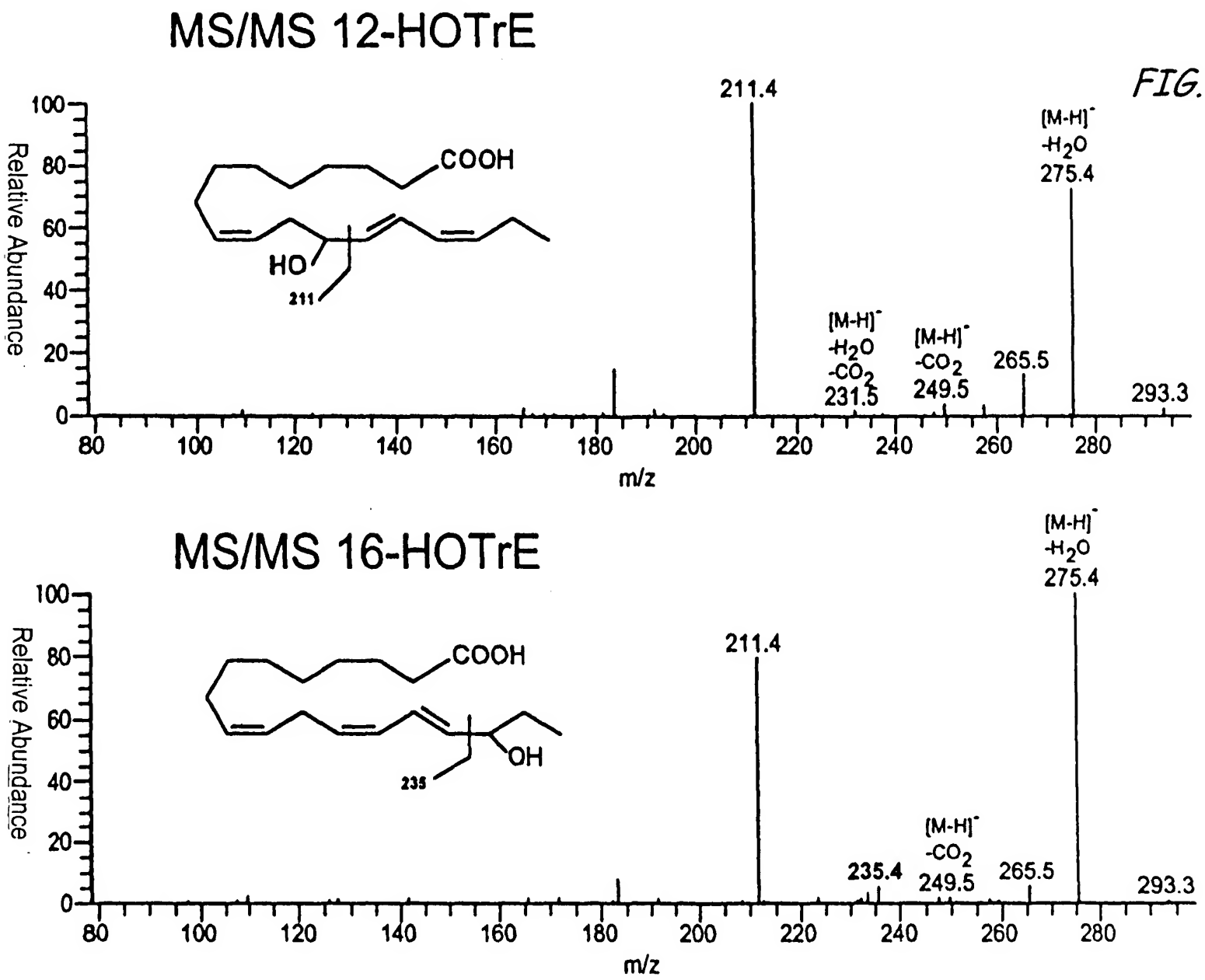

MS/MS 12-HOTrE
Relative Abundance
m/z
COOH
HO
211
211.4
[M-H]⁻ -H2O 275.4
[M-H]⁻ -H2O -CO2 231.5
[M-H]⁻ -CO2 249.5
265.5
293.3
MS/MS 16-HOTrE
Relative Abundance
m/z
COOH
OH
235
211.4
[M-H]⁻ -H2O 275.4
235.4
[M-H]⁻ -CO2 249.5
265.5
293.3

FIG. 10G

FIG. 10H

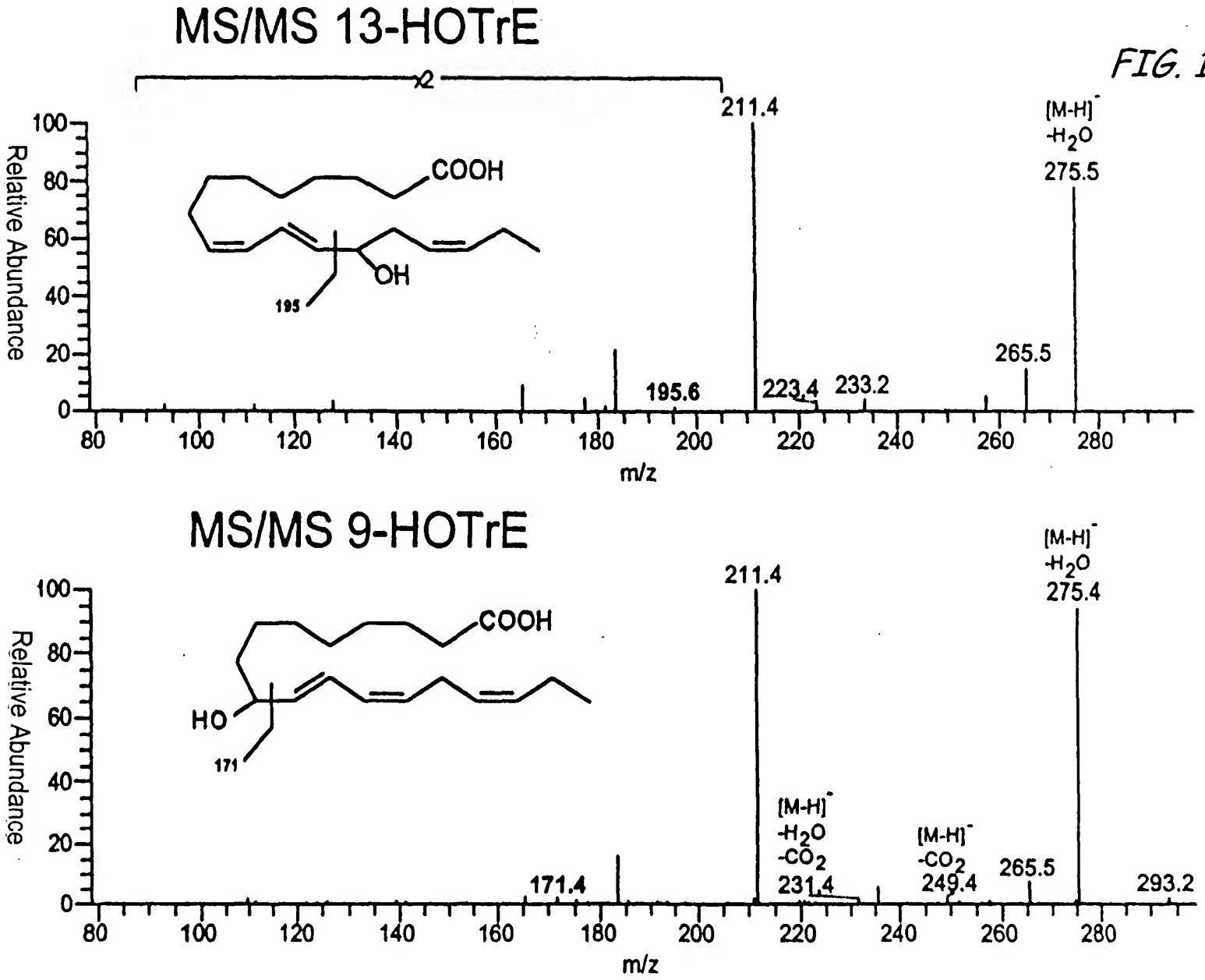

MS/MS 13-HOTrE
x2
211.4
[M-H]⁻
-H2O
275.5
COOH
OH
195
265.5
195.6
223.4
233.2
Relative Abundance
m/z
MS/MS 9-HOTrE
211.4
[M-H]⁻
-H2O
275.4
COOH
HO
171
[M-H]⁻
-H2O
-CO2
231.4
[M-H]⁻
-CO2
249.4
265.5
171.4
293.2
Relative Abundance
m/z

FIG. 10I

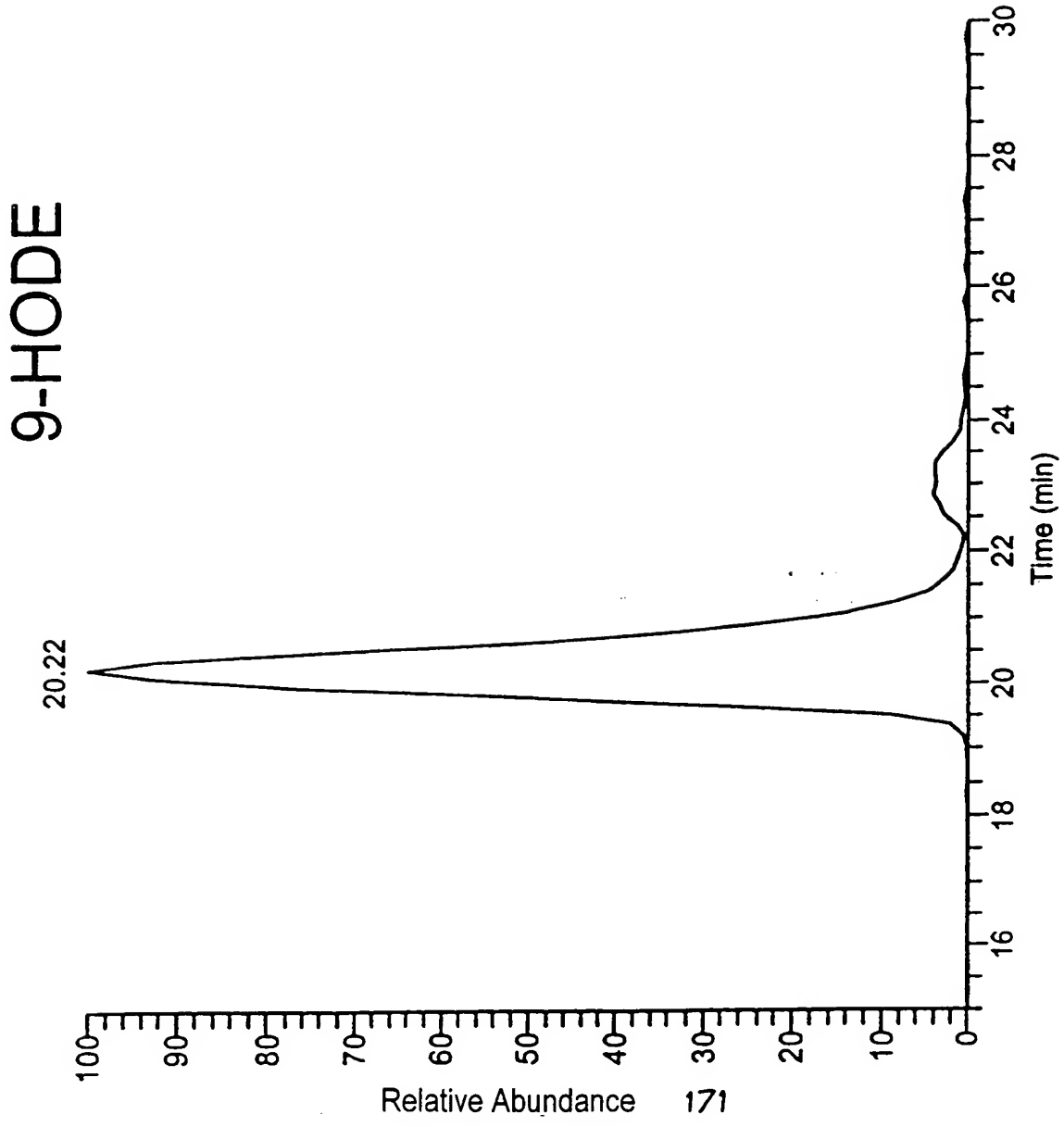

9-HODE
20.22
Relative Abundance
Time (min)
100
90
80
70
60
50
40
30
20
10
0
16
18
20
22
24
26
28
30
171

FIG. 10J

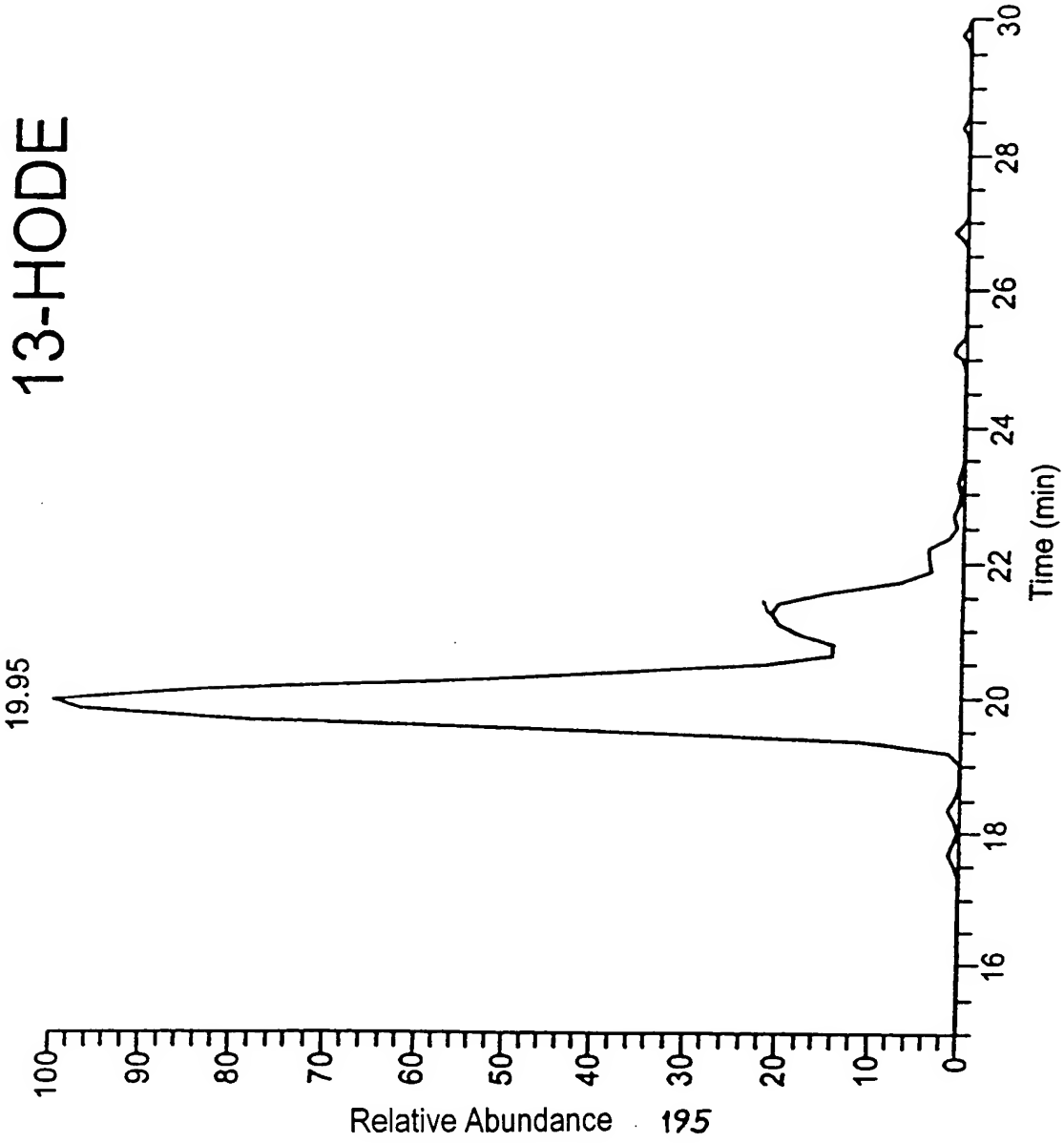

13-HODE
19.95
Relative Abundance
195
Time (min)
100
90
80
70
60
50
40
30
20
10
0
16
18
20
22
24
26
28
30

FIG. 10K

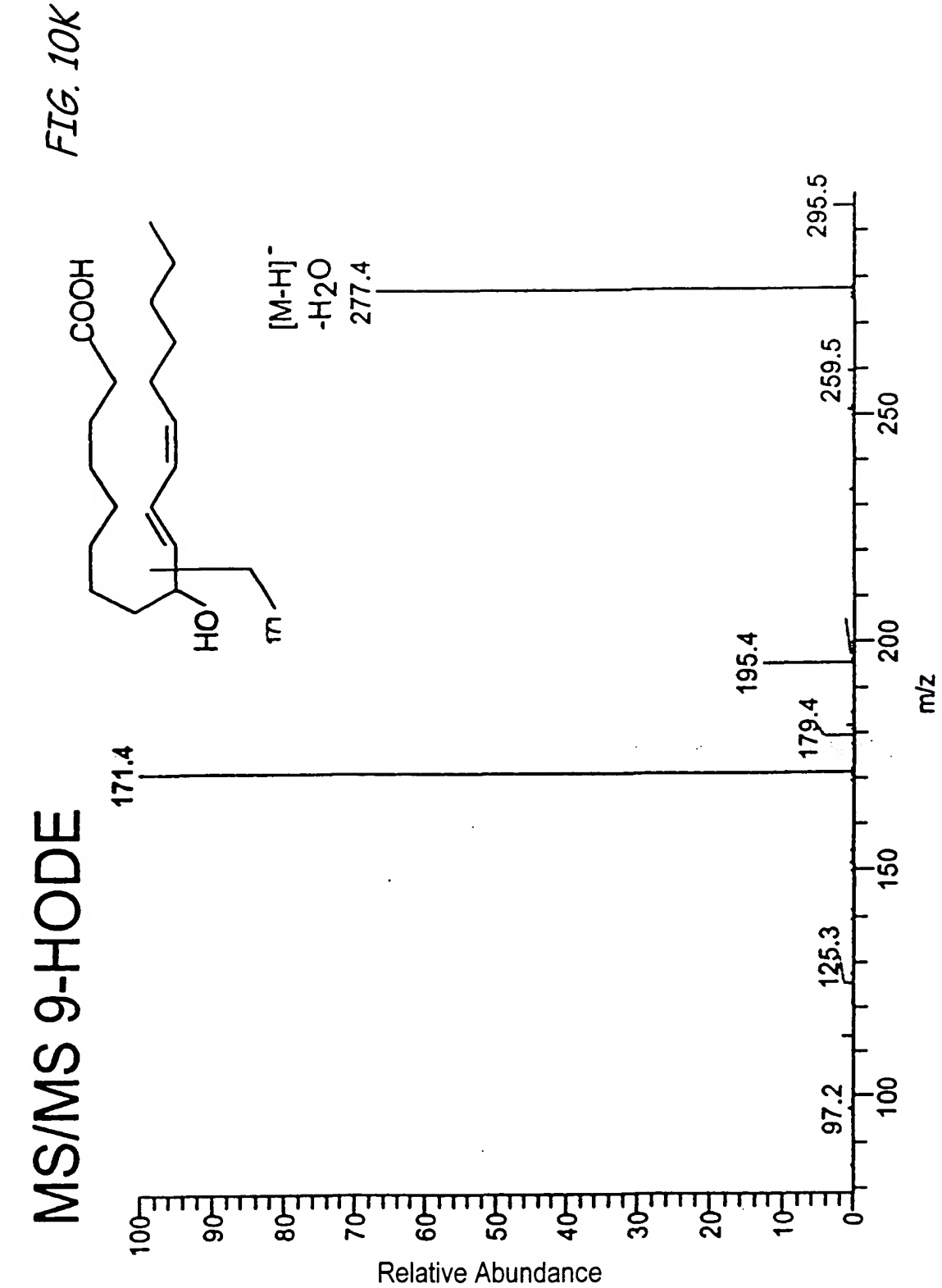
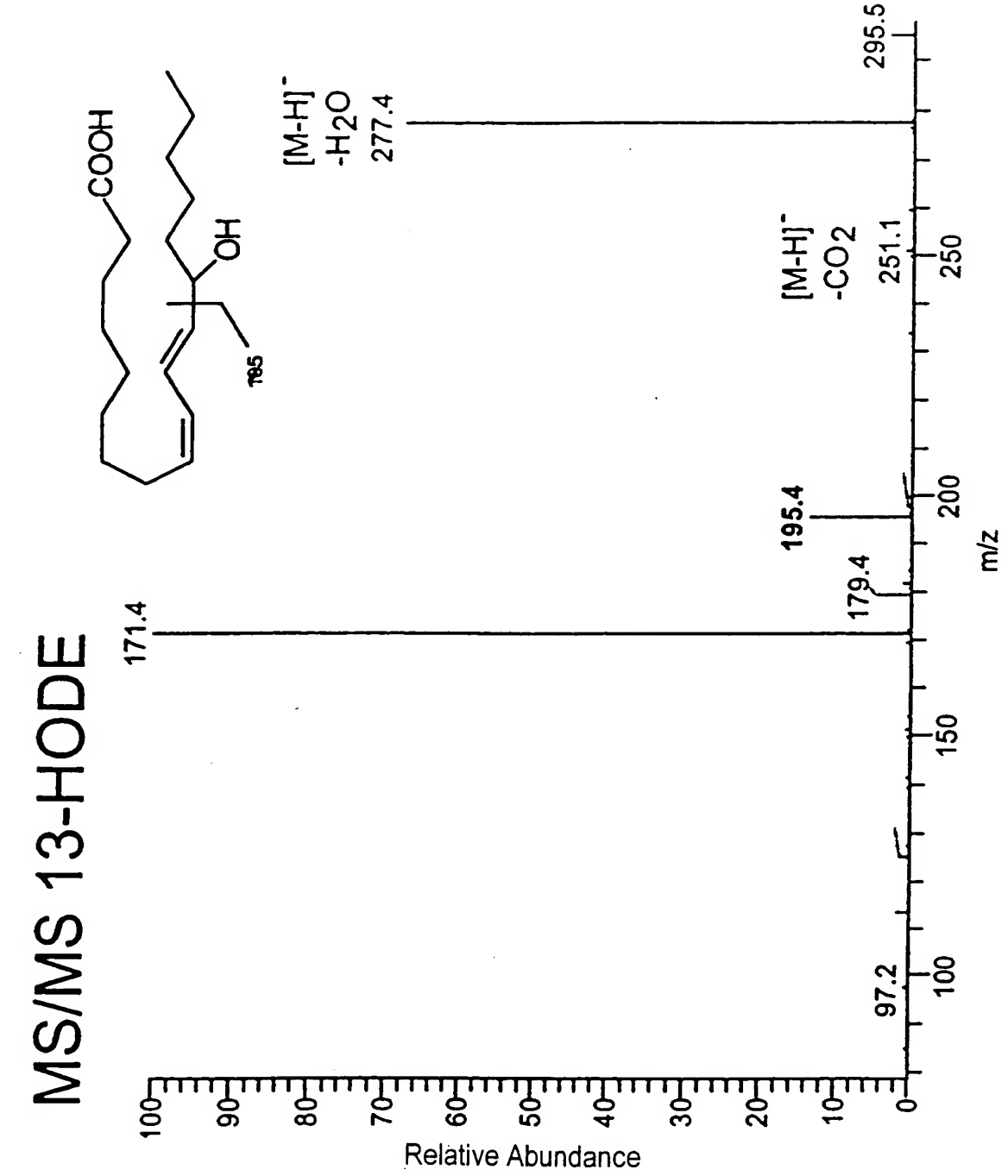

MS/MS 9-HODE
COOH
HO
[M-H]⁻
-H2O
277.4
171.4
195.4
179.4
125.3
97.2
295.5
259.5
Relative Abundance
m/z
100
90
80
70
60
50
40
30
20
10
0
100
150
200
250

FIG. 10L


MS/MS 13-HODE
COOH
OH
[M-H]⁻
-H2O
277.4
[M-H]⁻
-CO2
251.1
171.4
195.4
179.4
97.2
295.5
Relative Abundance
m/z
0
10
20
30
40
50
60
70
80
90
100
150
200
250

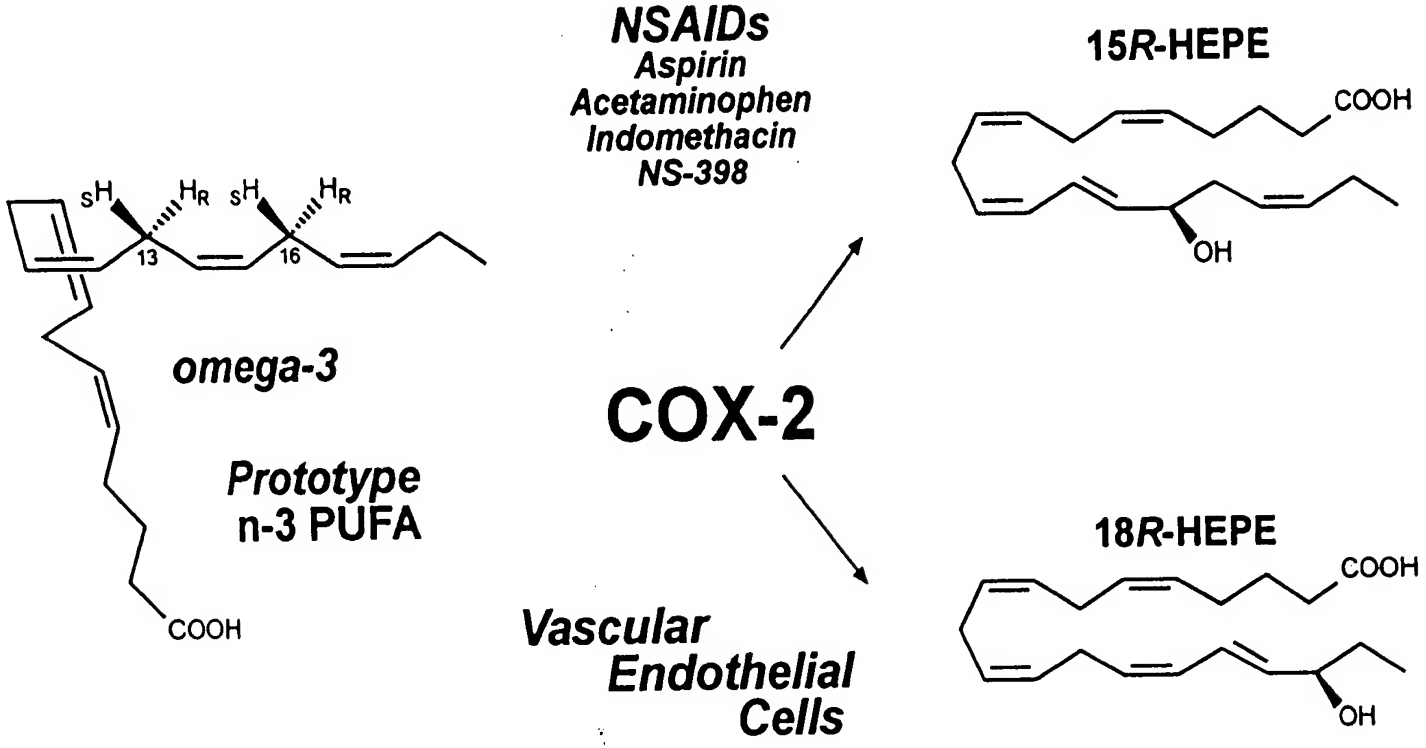

NSAIDs
Aspirin
Acetaminophen
Indomethacin
NS-398
15R-HEPE
COOH
OH
sH
HR
sH
HR
13
16
omega-3
Prototype
n-3 PUFA
COOH
COX-2
Vascular
Endothelial
Cells
18R-HEPE
COOH
OH

FIG. 11A

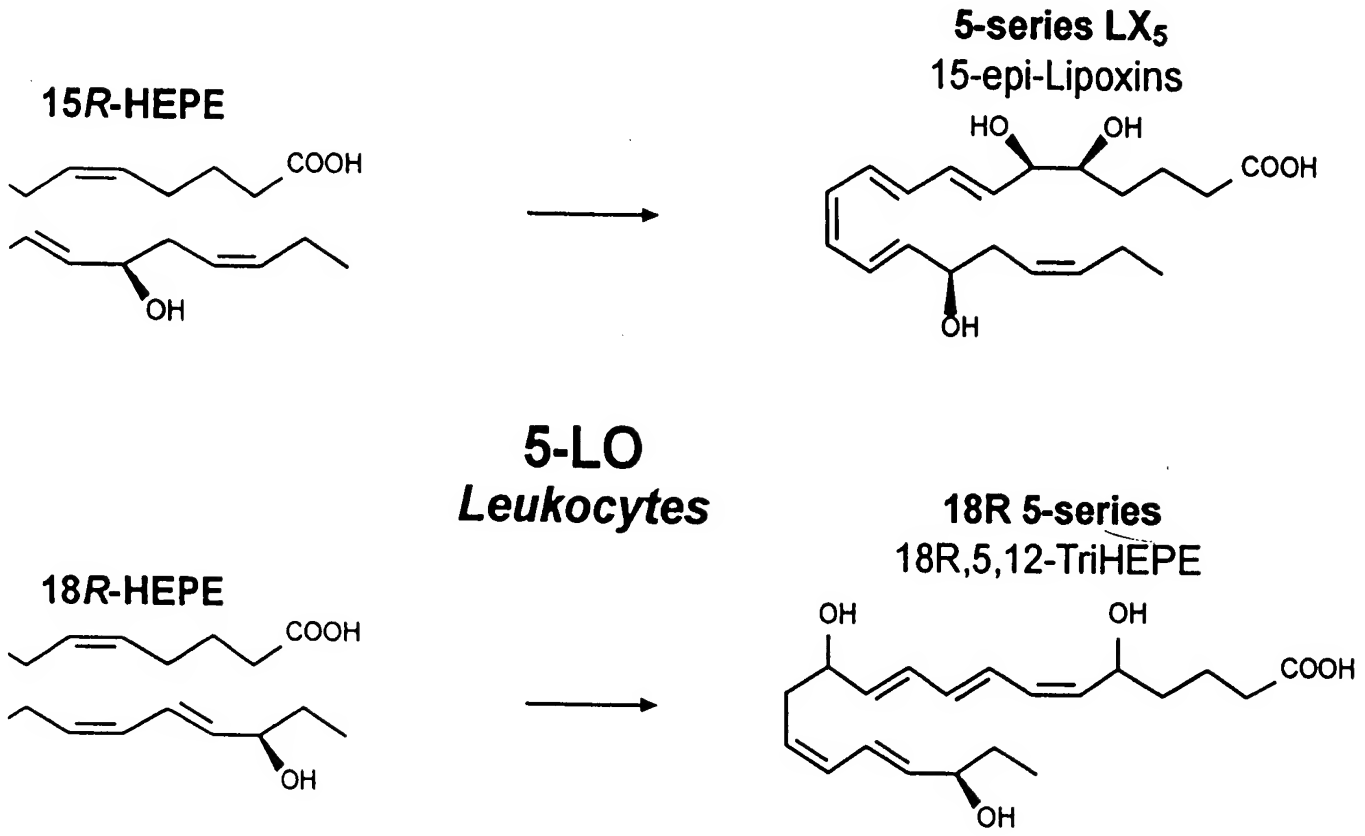

15R-HEPE
COOH
OH
5-series LX5
15-epi-Lipoxins
HO
OH
COOH
OH
5-LO
Leukocytes
18R-HEPE
COOH
OH
18R 5-series
18R,5,12-TriHEPE
OH
OH
COOH
OH

FIG. 11B

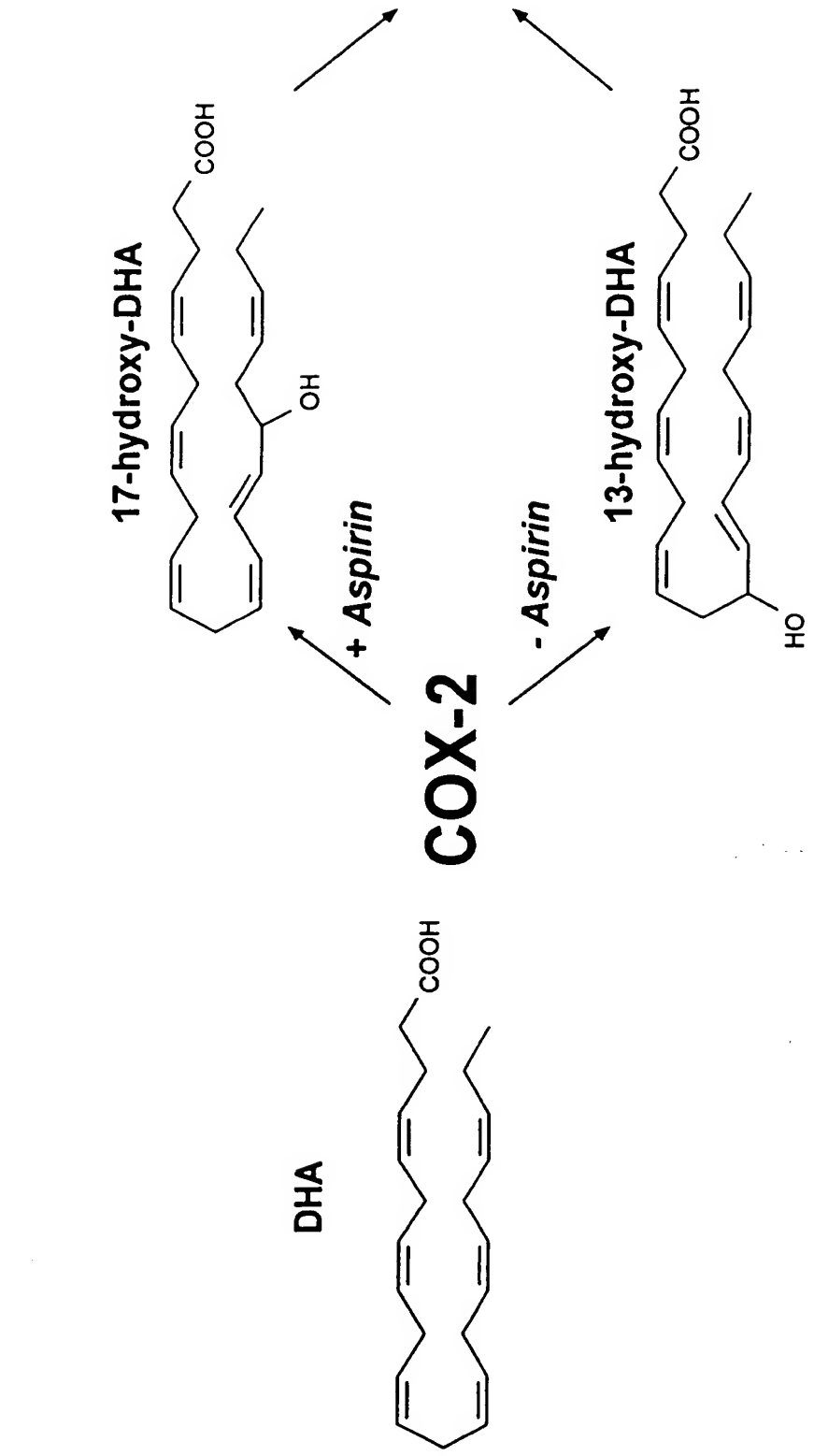
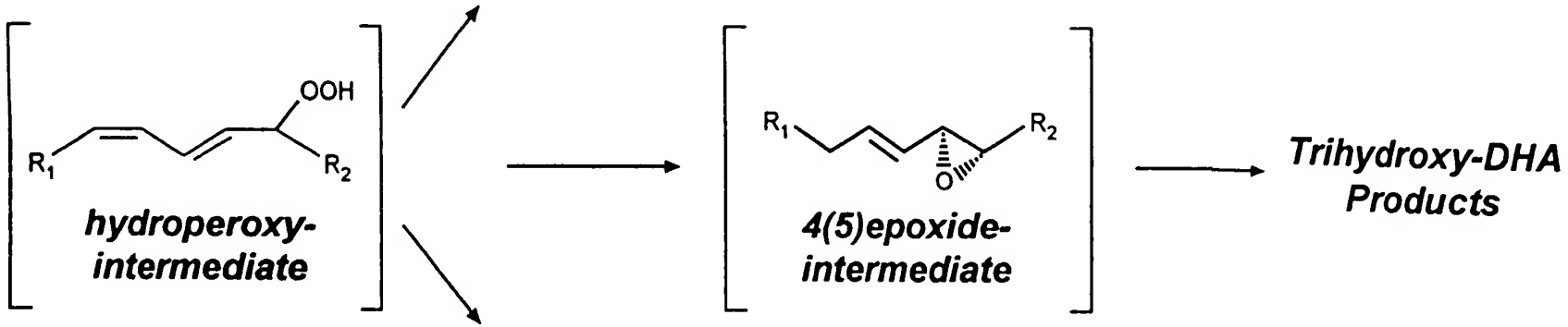

17-hydroxy-DHA
COOH
OH
+ Aspirin
COX-2
- Aspirin
13-hydroxy-DHA
COOH
HO
DHA
COOH

FIG. 11C

4,17-dihydroxy-DHA



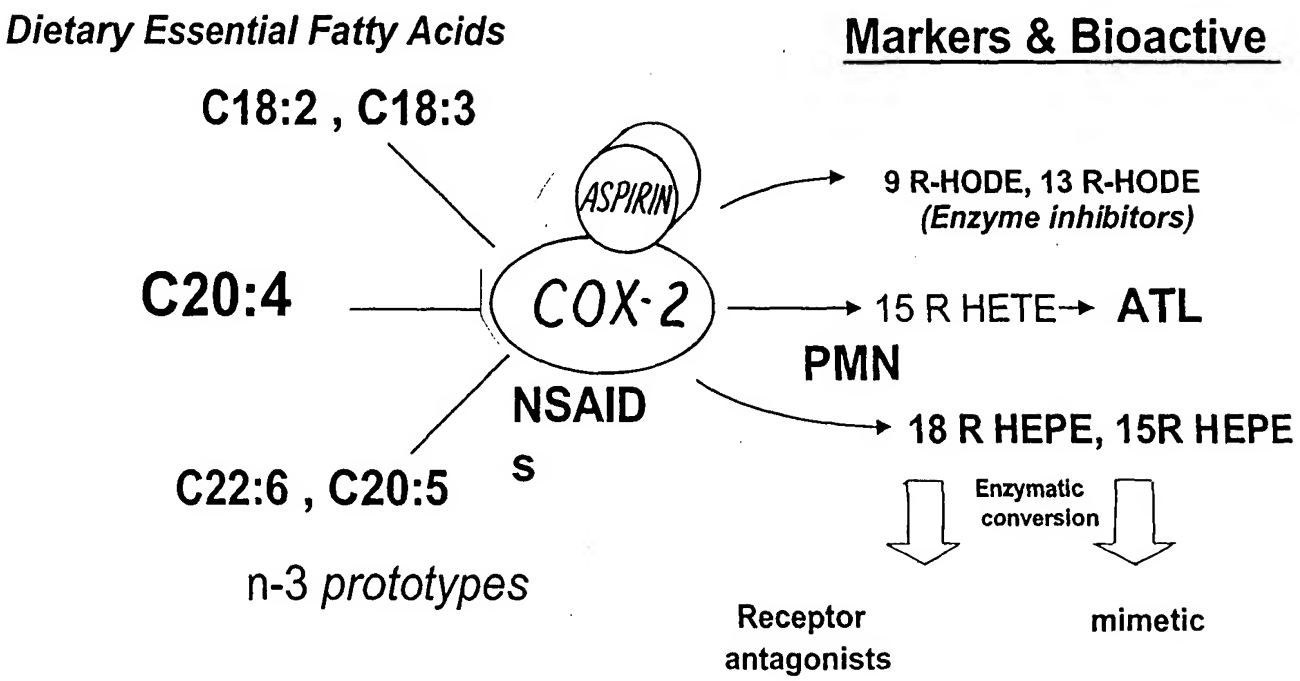
4,13-dihydroxy-DHA

5-LO
Leukocytes

FIG. 11D

FIG. 12

Aspirin Triggered / NSAIDs : New Pathways



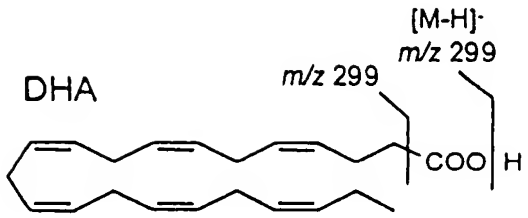
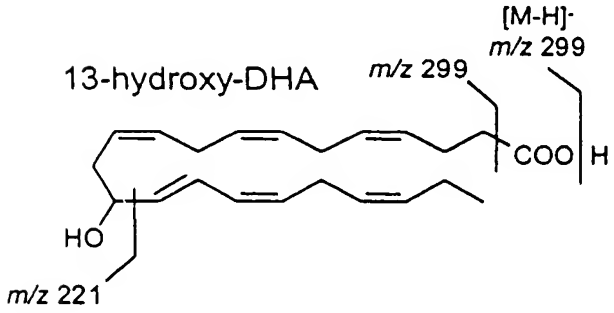
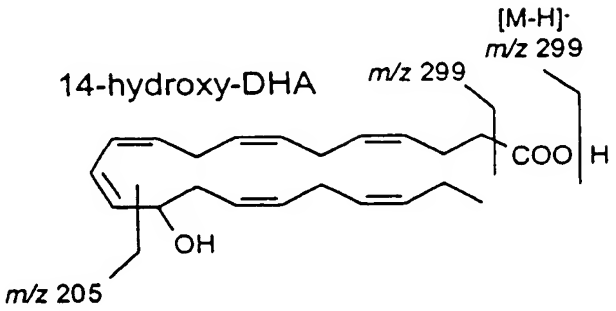


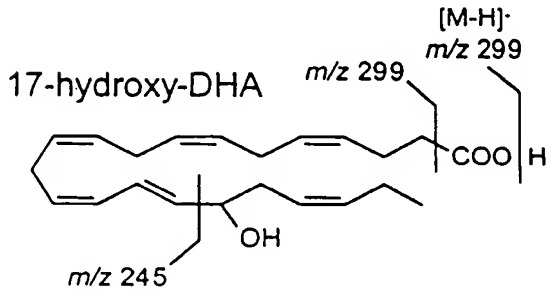
FIG. 13

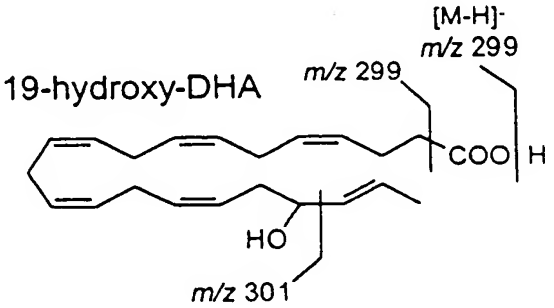
Major Products

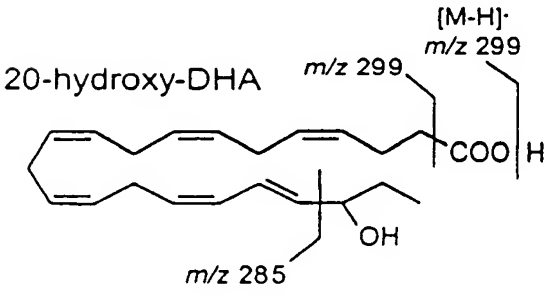
Minor Products











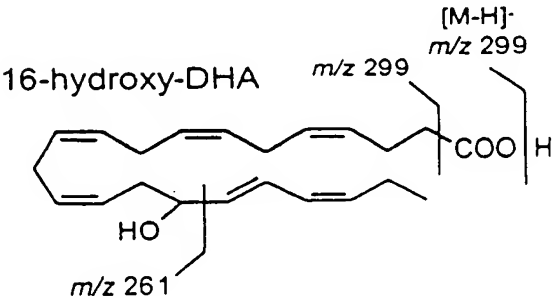


FIG. 14A

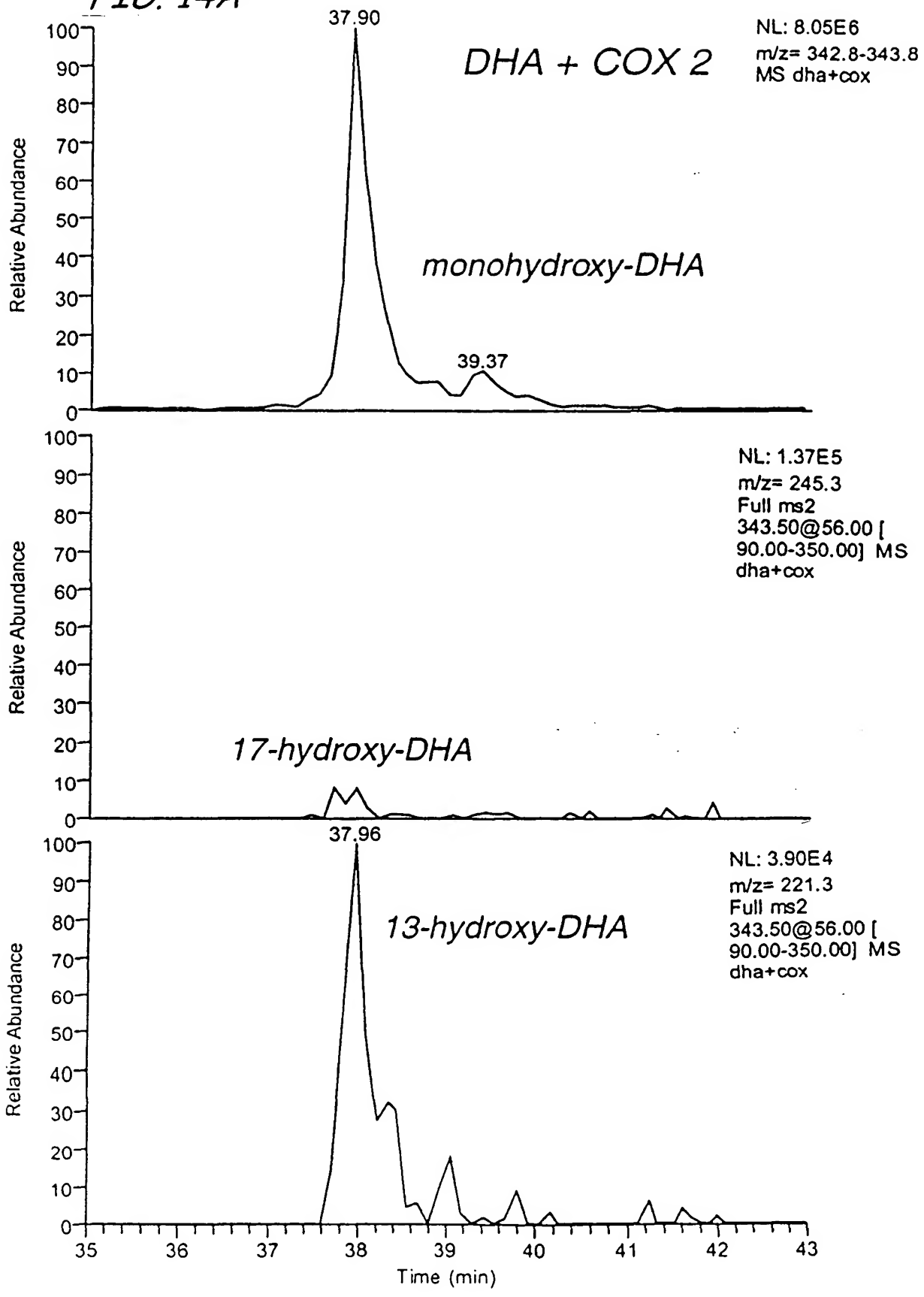
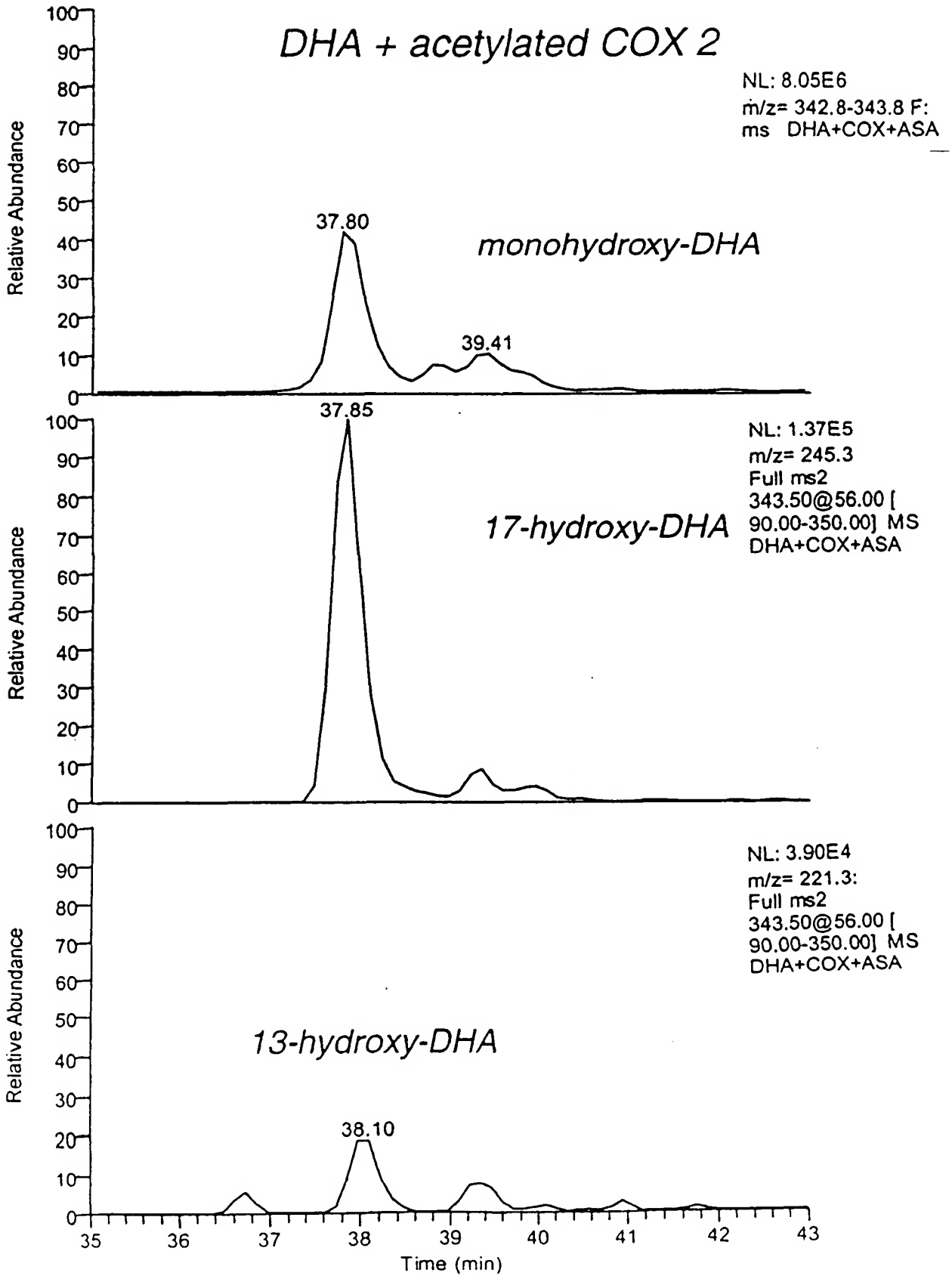

37.90
DHA + COX 2
NL: 8.05E6
m/z= 342.8-343.8
MS dha+cox
monohydroxy-DHA
39.37
Relative Abundance
NL: 1.37E5
m/z= 245.3
Full ms2
343.50@56.00 [
90.00-350.00] MS
dha+cox
17-hydroxy-DHA
37.96
NL: 3.90E4
m/z= 221.3
Full ms2
343.50@56.00 [
90.00-350.00] MS
dha+cox
13-hydroxy-DHA
Time (min)

FIG. 14B


DHA + acetylated COX 2
NL: 8.05E6
m/z= 342.8-343.8 F:
ms DHA+COX+ASA
37.80
monohydroxy-DHA
39.41
Relative Abundance
37.85
NL: 1.37E5
m/z= 245.3
Full ms2
343.50@56.00 [
90.00-350.00] MS
DHA+COX+ASA
17-hydroxy-DHA
NL: 3.90E4
m/z= 221.3:
Full ms2
343.50@56.00 [
90.00-350.00] MS
DHA+COX+ASA
13-hydroxy-DHA
38.10
Time (min)

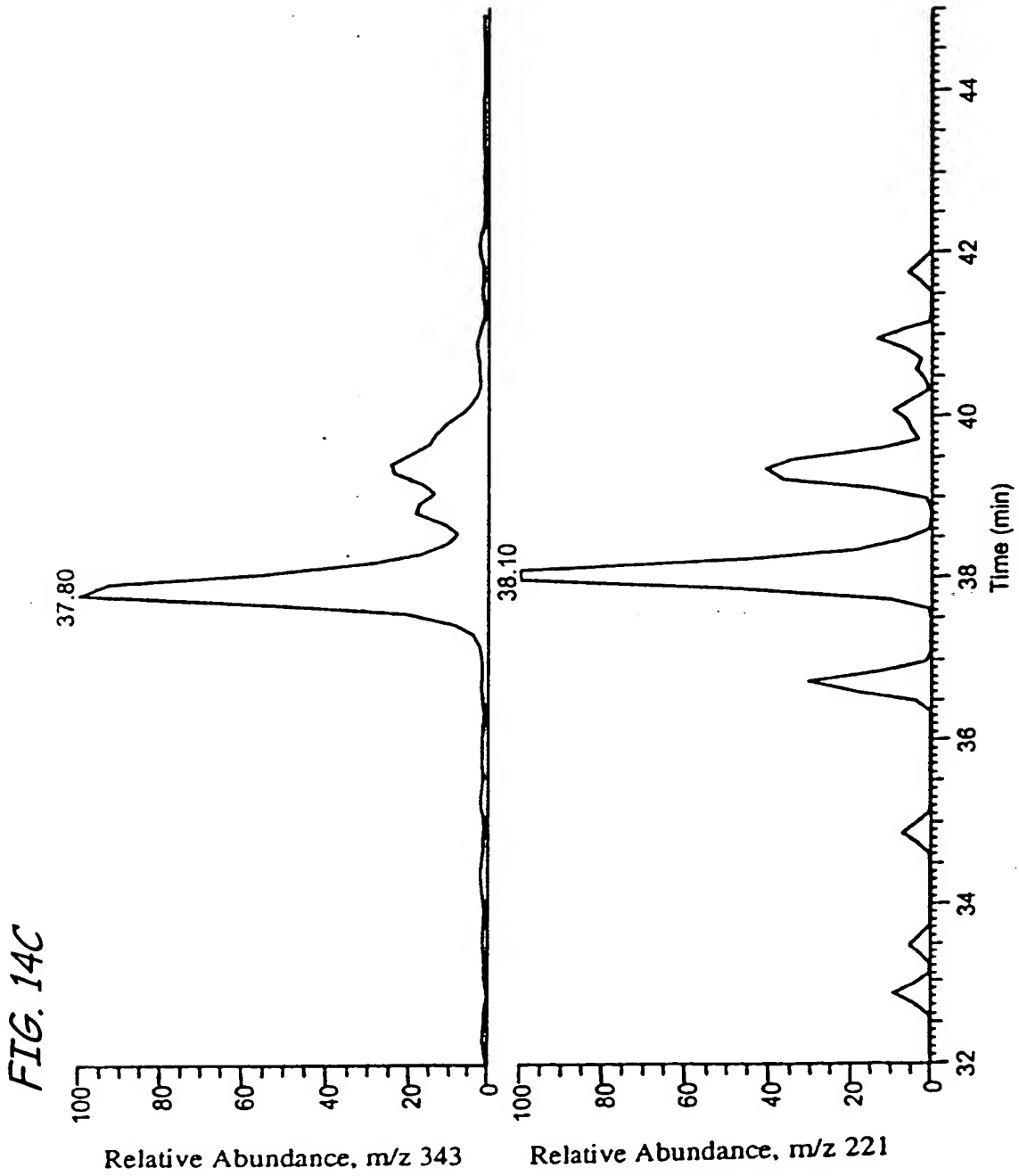
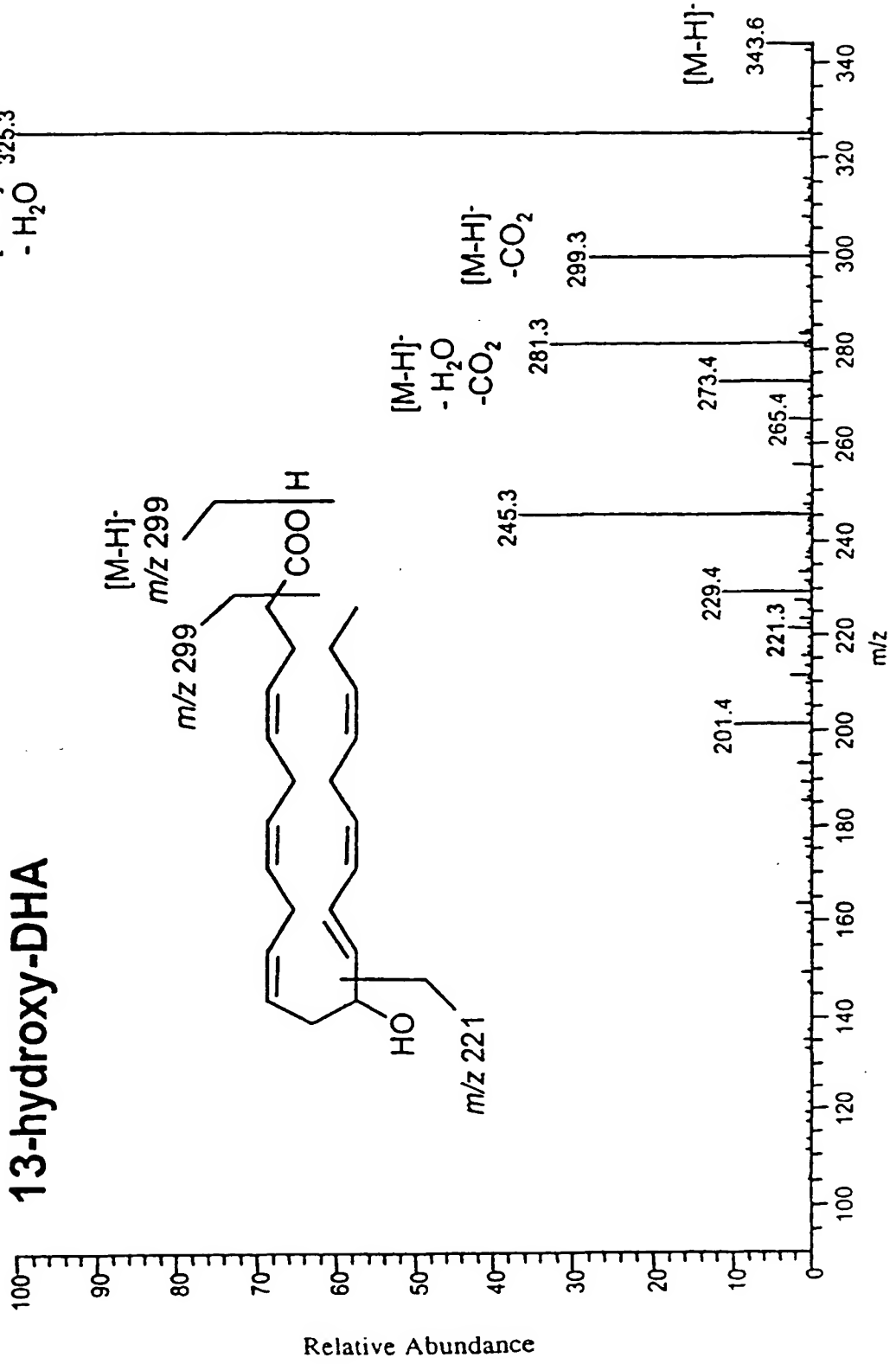

37.80
38.10
100
80
60
40
20
0
Relative Abundance, m/z 343
Relative Abundance, m/z 221
32
34
36
38
40
42
44
Time (min)

FIG. 14C

FIG. 14D


13-hydroxy-DHA
[M-H]- m/z 299
m/z 299
COO
H
HO
m/z 221
[M-H]- - H2O
325.3
[M-H]- - H2O -CO2
281.3
[M-H]- -CO2
299.3
245.3
273.4
265.4
229.4
221.3
201.4
[M-H]-
343.6
Relative Abundance
m/z

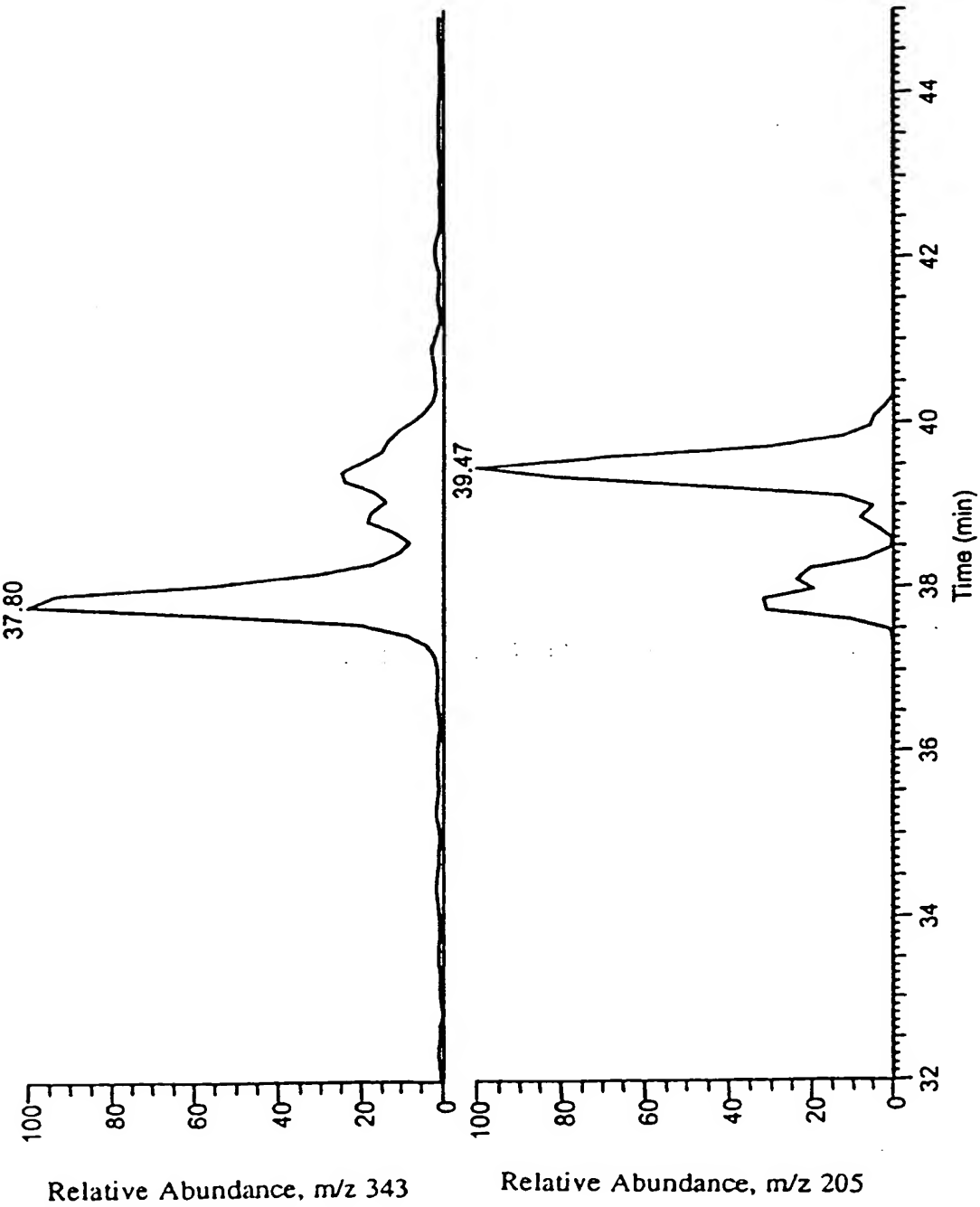

37.80
39.47
100
80
60
40
20
0
Relative Abundance, m/z 343
Relative Abundance, m/z 205
32
34
36
38
40
42
44
Time (min)

FIG. 14E

FIG. 14F

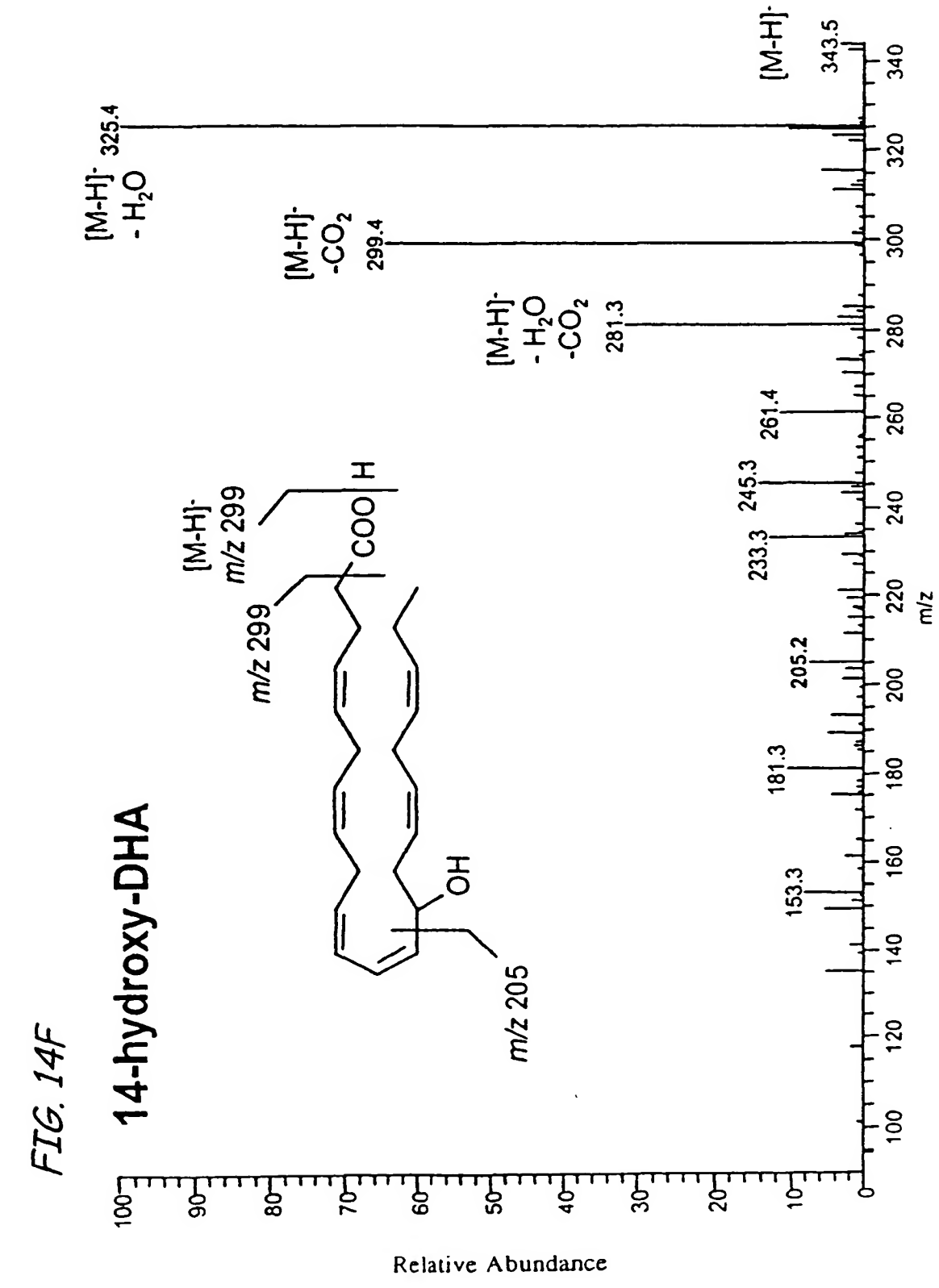

14-hydroxy-DHA
[M-H]- 325.4
- H2O
[M-H]-
-CO2
299.4
[M-H]-
- H2O
-CO2
281.3
[M-H]-
343.5
261.4
245.3
233.3
205.2
181.3
153.3
[M-H]-
m/z 299
m/z 299
COO
H
OH
m/z 205
Relative Abundance
m/z
0
10
20
30
40
50
60
70
80
90
100
100
120
140
160
180
200
220
240
260
280
300
320
340

FIG. 14G

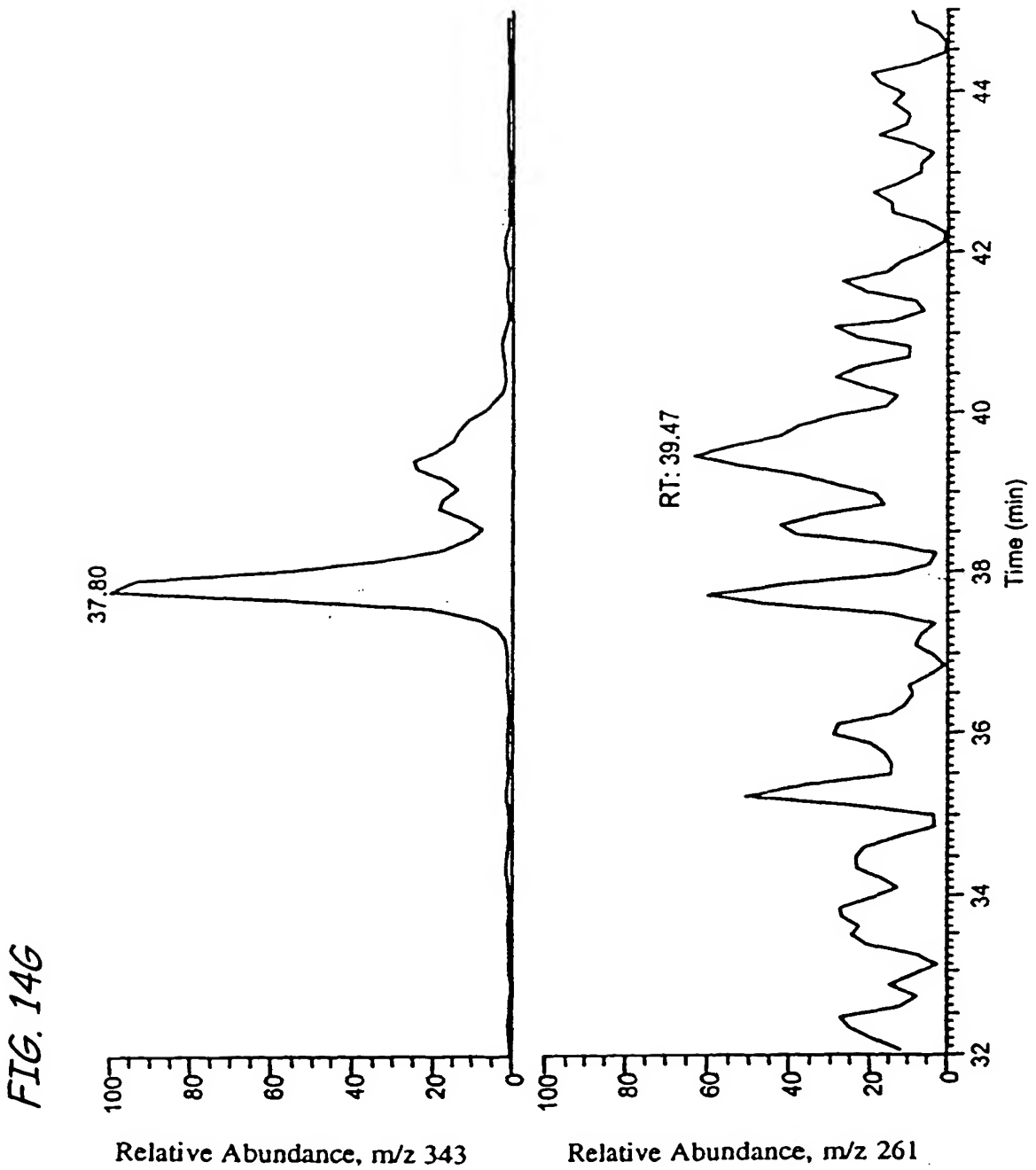
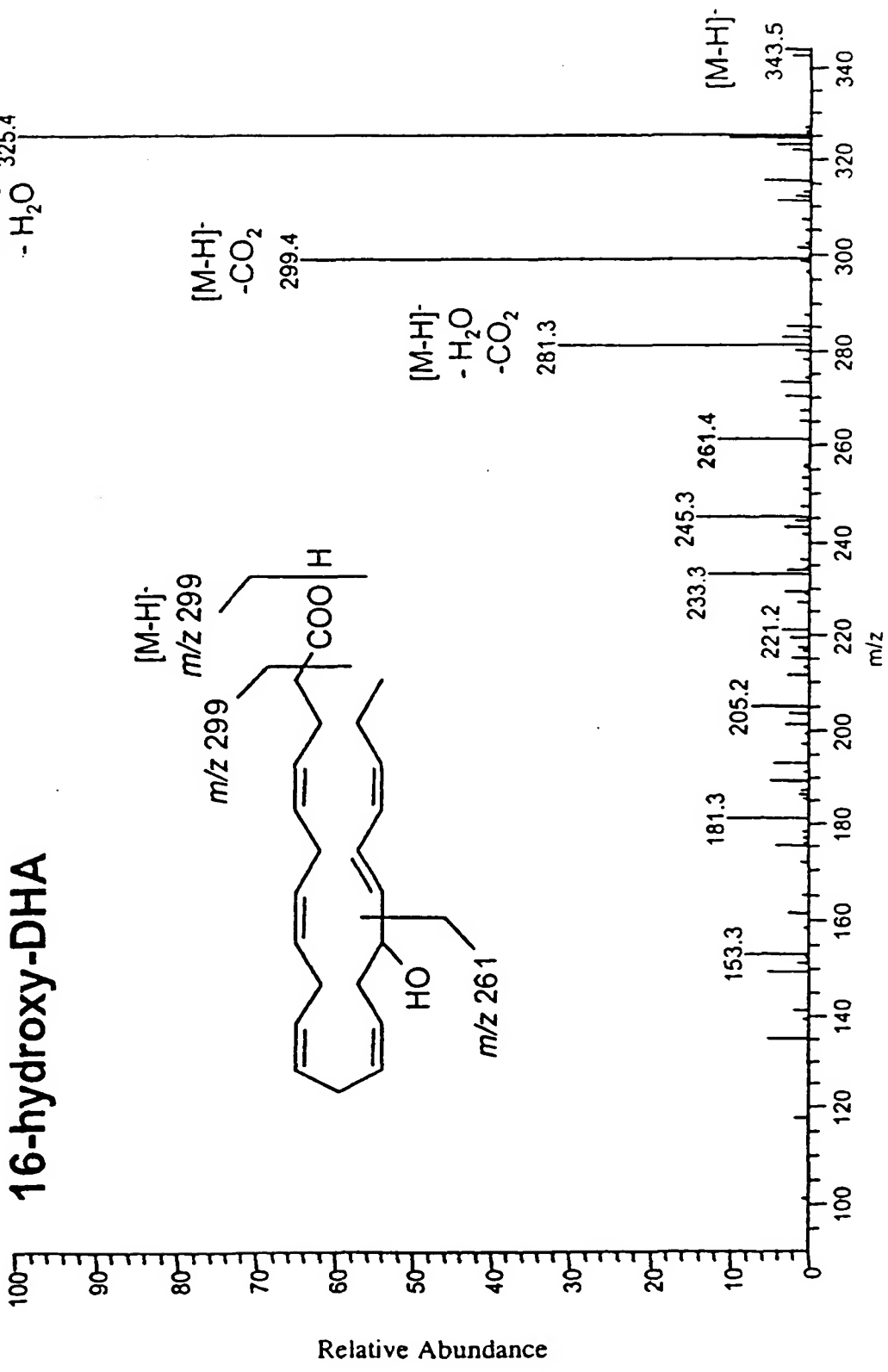

37.80
RT: 39.47
100
80
60
40
20
0
32
34
36
38
40
42
44
Time (min)
Relative Abundance, m/z 343
Relative Abundance, m/z 261

FIG. 14H


16-hydroxy-DHA
[M-H]- - H2O 325.4
[M-H]- -CO2 299.4
[M-H]- - H2O -CO2 281.3
[M-H]- 343.5
261.4
245.3
233.3
221.2
205.2
181.3
153.3
[M-H]- m/z 299
m/z 299
COO
H
HO
m/z 261
Relative Abundance
m/z

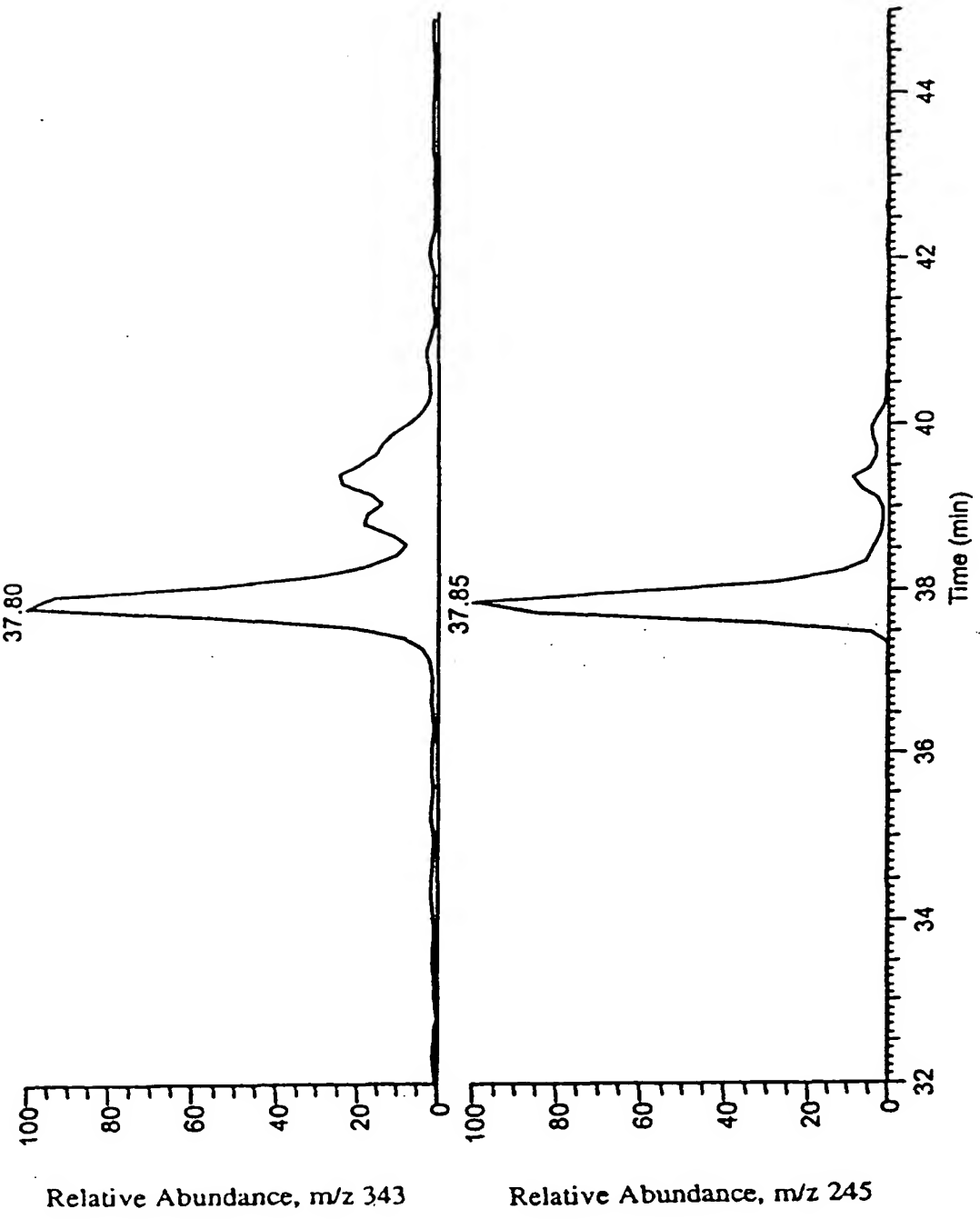
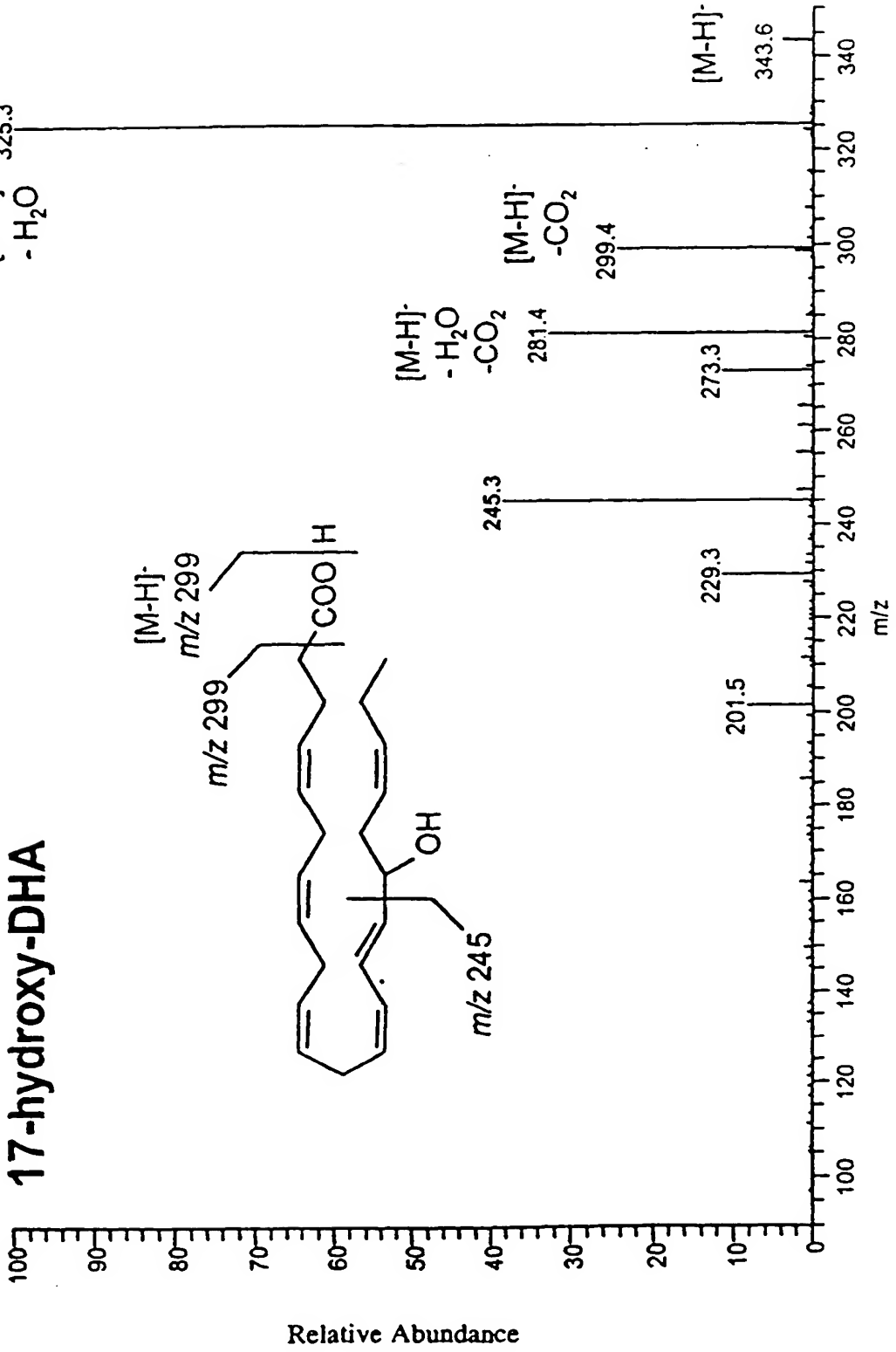

37.80
37.85
100
80
60
40
20
0
32
34
36
38
40
42
44
Time (min)
Relative Abundance, m/z 343
Relative Abundance, m/z 245

FIG. 14I

FIG. 14J


17-hydroxy-DHA
[M-H]- - H2O
325.3
[M-H]- m/z 299
m/z 299
COO
H
OH
m/z 245
[M-H]- - H2O -CO2
281.4
[M-H]- -CO2
299.4
245.3
229.3
273.3
201.5
[M-H]-
343.6
Relative Abundance
m/z

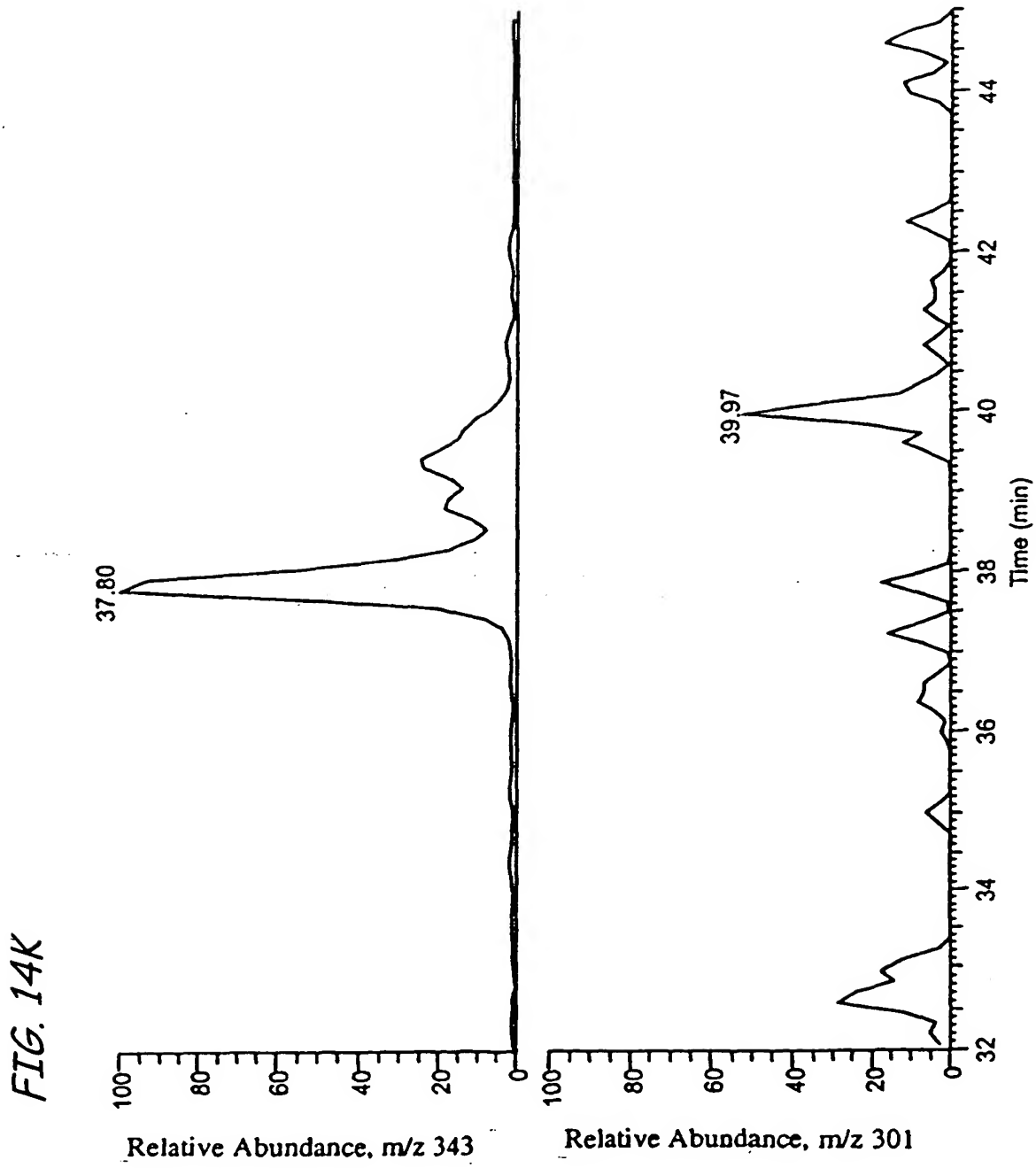
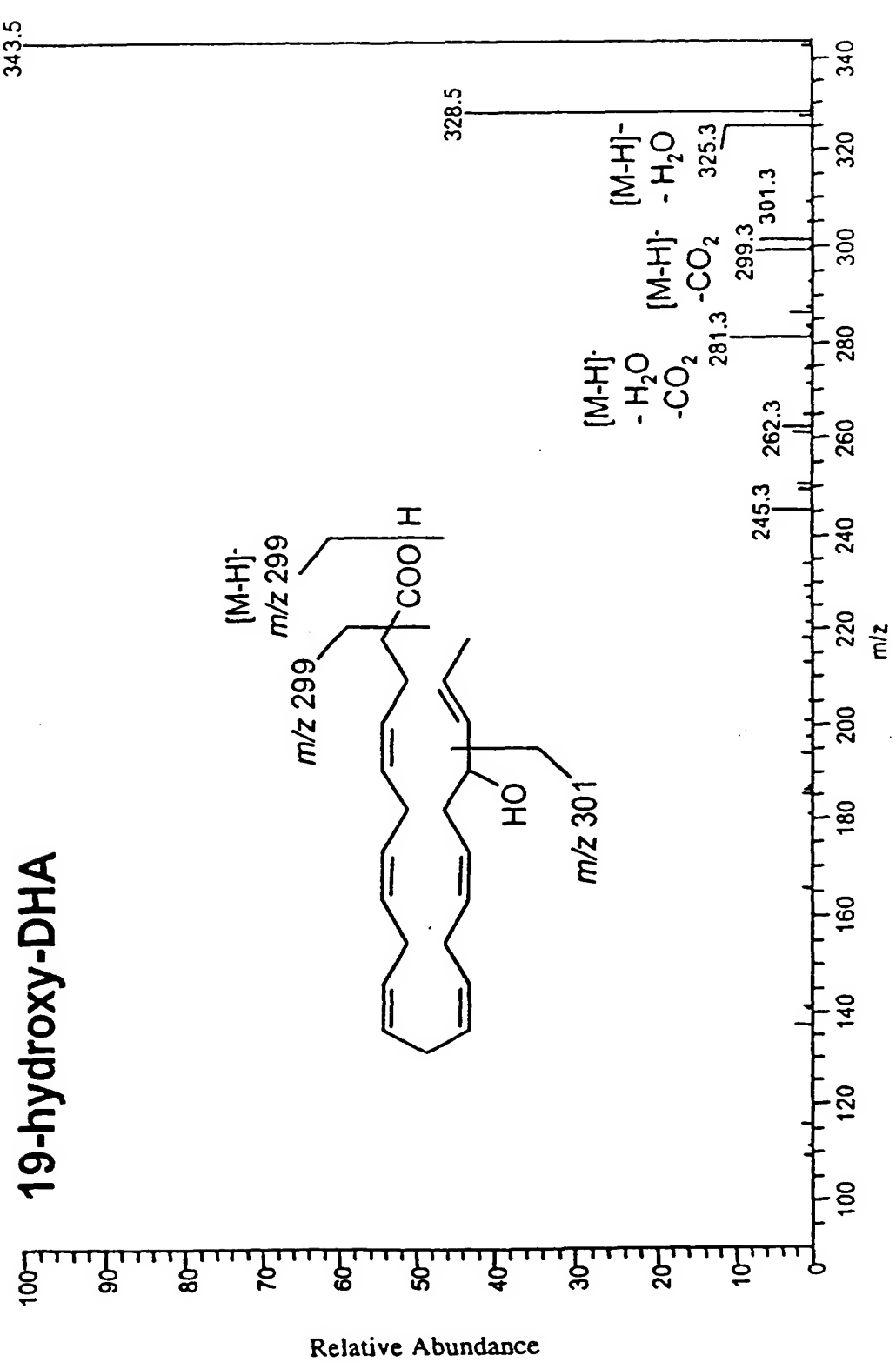

37.80
39.97
100
80
60
40
20
0
32
34
36
38
40
42
44
Time (min)
Relative Abundance, m/z 343
Relative Abundance, m/z 301

FIG. 14K

FIG. 14L


19-hydroxy-DHA
[M-H]-
343.5
328.5
[M-H]- - H2O
325.3
[M-H]- -CO2
301.3
299.3
[M-H]- - H2O -CO2
281.3
262.3
245.3
[M-H]- m/z 299
m/z 299
COO
H
HO
m/z 301
Relative Abundance
m/z

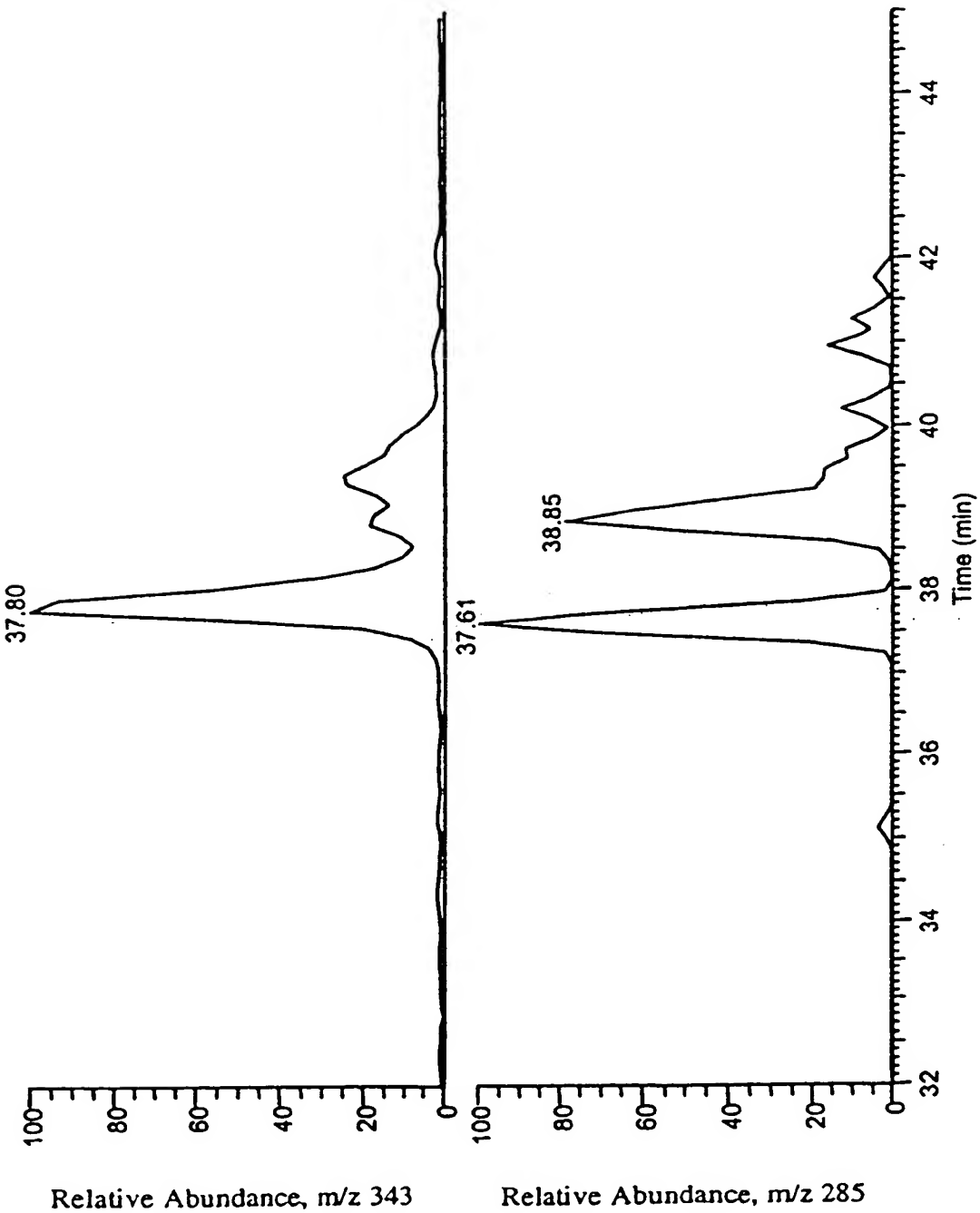

37.80
37.61
38.85
100
80
60
40
20
0
32
34
36
38
40
42
44
Time (min)
Relative Abundance, m/z 343
Relative Abundance, m/z 285

FIG. 14M

FIG. 14N

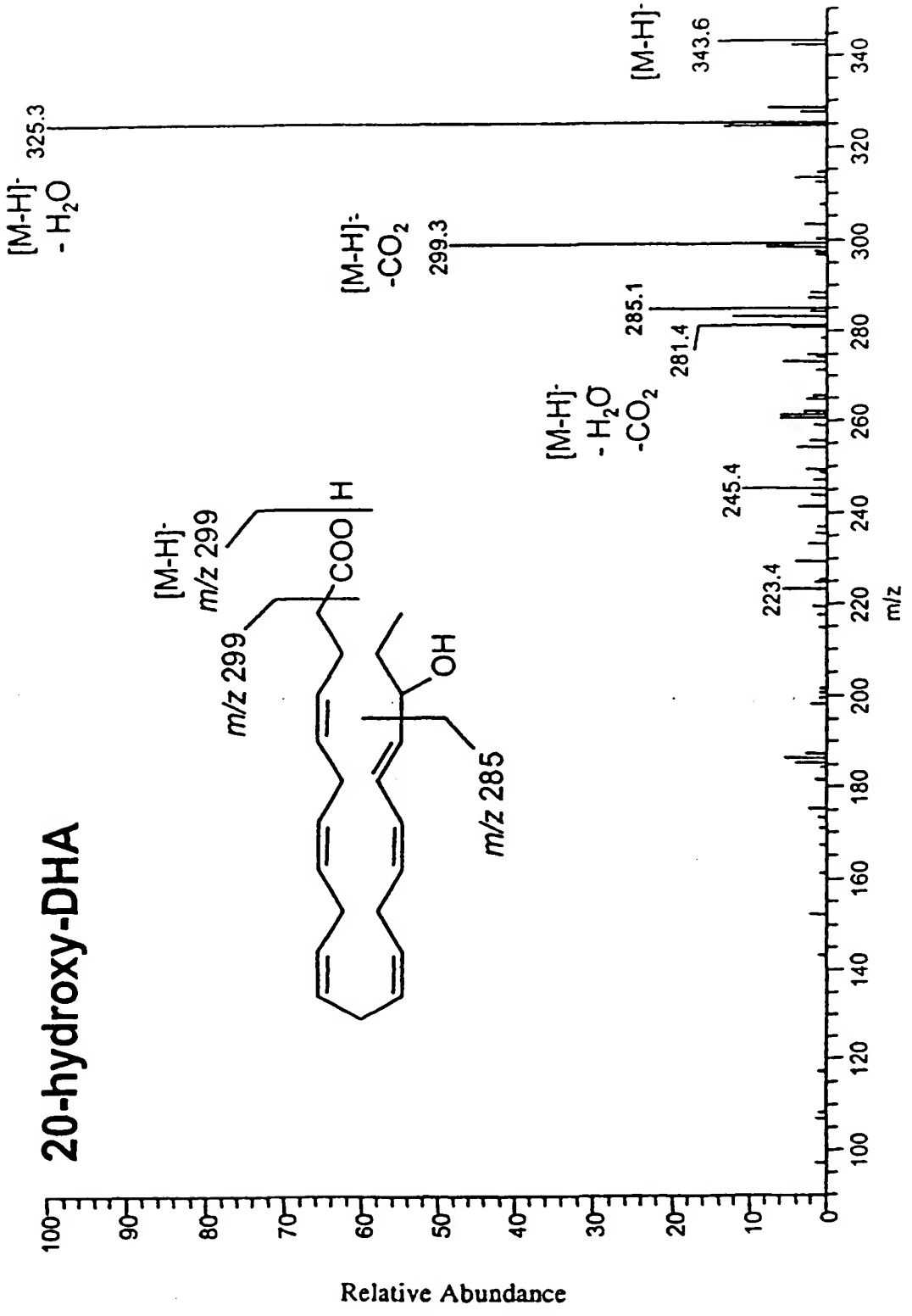
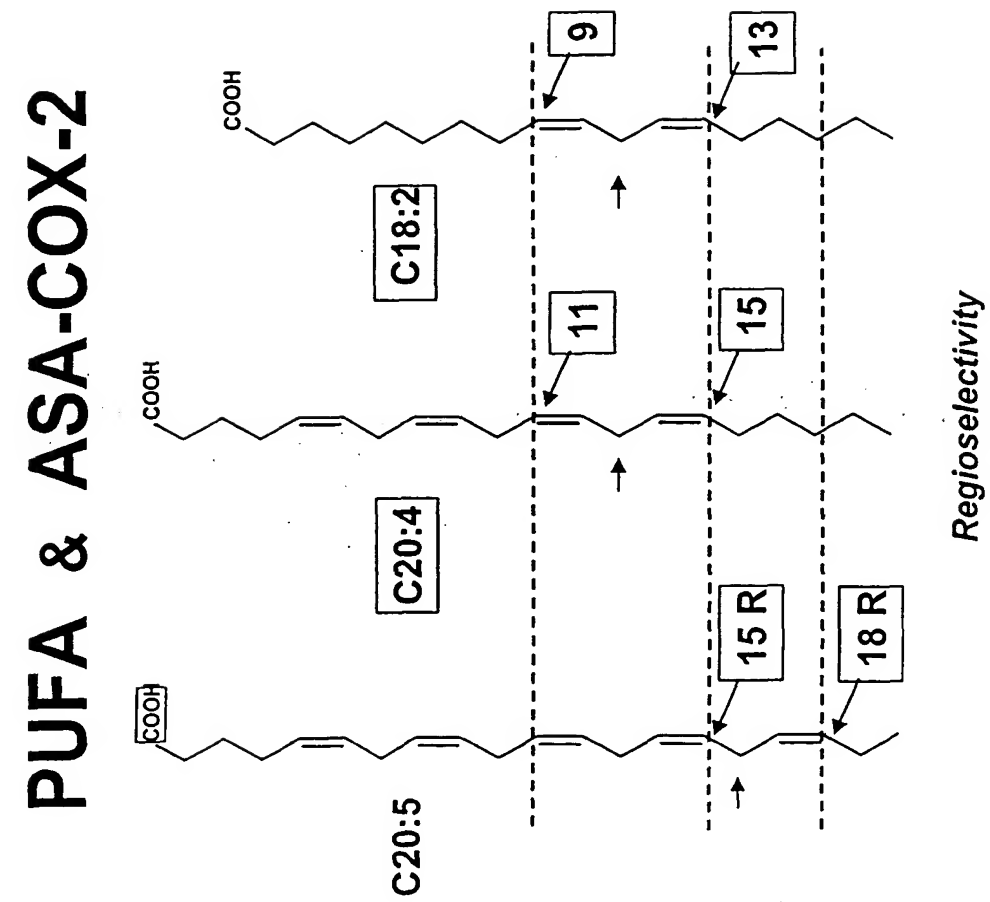

20-hydroxy-DHA
Relative Abundance
m/z
[M-H]- - H2O
325.3
[M-H]- -CO2
299.3
[M-H]- - H2O -CO2
285.1
281.4
245.4
223.4
[M-H]-
343.6
[M-H]- m/z 299
m/z 299
COOH
OH
m/z 285

FIG. 15


PUFA & ASA-COX-2
COOH
C20:5
C20:4
C18:2
9
11
13
15
15 R
18 R
Regioselectivity